THE HONG KONG 香港醫訊
MEDICAL DIARY
www.fmshk.org
VOL.21 NO.2 February 2016

Clinical Pharmacology

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

BRINTELLIX TAKES CARE OF MORE THAN MOOD

- Brintellix is a new antidepressant with **Multimodal Activity**[1,4]
- Brintellix is efficacious in treating all the symptoms of depression (assessed by MADRS) across a range of patients[2-5]
- Brintellix also significantly improves cognitive performance in depressed patients and reduces the cognitive symptoms of depression[2,9] that affect most patients[6]
  - **These include: concentration difficulties, poor attention, problems with memory and difficulty planning**[6-8]
- Brintellix is well tolerated[4,5,10-12]
- Patients (18-65 yrs) can start, stay and stop on Brintellix 10 mg once daily[4]

References:
1. Bang-Andersen B et al. J Med Chem. 2011; 54(9): 3206-3221. 2. Katona C et al. Int Clin Psychopharmacol. 2012; 27(4): 215-223. 3. Dragheim M, Nielsen R. A randomized, double-blind, study of vortioxetine versus agomelatine in adults with major depressive disorder (MDD) switched after inadequate response to SSRI or SNRI treatment. Poster presented at the 53rd NCDEU meeting, May 28-31, 2013, Hollywood, Florida, USA. 4. Brintellix. Summary of Product Characteristics. 2013. 5. Alvarez E et al. Int J Neuropsychopharmacol. 2012; 15(5): 589-600.. 6. Conradi HJ et al. Psychol Med. 2011; 41: 1165-1174. 7. Hammar A, Ardal G. Front Hum Neurosci. 2009; 3: 26. 8. Marazziti D et al. Eur J Pharmacol. 2010; 626(1): 83-86. 9. McIntyre R, et al. Randomized, double-blind, placebo-controlled study of the efficacy of vortioxetine on cognitive function in adult patients with major depressive disorder (MDD). Poster presented at the 52nd Annual Meeting of the American College of Neuropsychopharmacology (ACNP), December 8-12, 2013, Hollywood, Florida, USA.. 10. Baldwin DS et al. Eur Neuropsychopharmacol. 2012; 22(7): 482-491. 11. Boulenger JP et al. J Psychopharmacol. 2012; 26(11): 1408-1416. 12. Henigsberg N et al. J Clin Psychiatry. 2012; 73(7): 953-959.

Lundbeck

Contents

Disclaimer

The Cover Shot

A willow tree-lined alley in Yunnan, dotted with pink flowers of the ***rosacea*** family (薔薇).

In Chinese culture, willow represents elegance and charm. Its branches and leaves sway gracefully in the wind. Its vitality makes it easy to grow and it is often associated with the Spring season. Its bark has long been known to Chinese and ancients including Hippocrates as a remedy for aches and fever, for it contains salicin which is metabolised into salicylic acid in the human body.

Dr Kin-lun TSANG
Specialist in Neurology

Chinese New Year Message from the President

Dr Mario WK CHAK

President
The Federation of Medical Societies of Hong Kong

Dr Mario WK CHAK

To start the Chinese New Year, I would like to share with you all a proverb from a famous ancient Chinese philosopher Kongzi.〈荀子· 哀公〉知不務多，務審其所知；言不務多，務審其所謂；行不務多，務審其所由.'One does not have to know everything, but he has to make sure what he knows is right; one does not have to talk a lot, but he has to be sure what he talks about is suitable; one does not have to do a lot, but he has to be sure what he does is reasonable.' This famous quote of Chinese wisdom advises that people do not have to know, talk or do a lot. It is more important to be sure that what one knows, says, and does are right, appropriate and justified. Although written many years ago, this proverb continues to convey words of great wisdom and a moral message.

In the present computer age, everyone can easily retrieve information from the internet through a computer or mobile phone. In the present world of exploding knowledge, we have no problem in accessing the most current information. Nonetheless it is important to differentiate what is right; what is wrong and how to apply information correctly in our daily life. The above traditional wisdom is applied by the medical and health professionals today in the practice of evidence-based medicine, as well as the practice of personalised /precision medicine that was recently advocated by U.S. President Barack Obama who said "Personalised Medicine gives us one of the greatest opportunities for new medical breakthroughs we never seen".

A period of rapid advances in technology has provided a golden opportunity to gather useful data relating to a range of potentially important disease determinants in clinical decision making. Access to detailed data will enable medicine to evolve from a one-size-fits-all/trial and error model that is associated with variable clinical effectiveness and a high rate of side effects to a model that provides a precision approach, healthcare based on an understanding of the patient's biological needs and heterogeneity, where treatment is individualized with consequent improved effectiveness and minimal side effects.

In model of precision/ personalised medicine, diagnostic test usually required to select an appropriate and optimal treatment according to a patient's genetic or microbiota make up or molecular or other relevant investigation results.

Precision medicine has been successfully applied in oncology and will soon be extended to other medical fields. It is undoubtedly a great revolution in existing medical care and heralds a new era of medicine.

As medical and health professionals, can we maintain the status quo? I think all of us realise that avoiding change today will only postpone necessary change and exacerbate existing weakness. But how? I realise that the importance for any one of you to be actively involved in your related medical society early in your career; you will gain not only medical knowledge but grow your professional enthusiasm. In joining the Federation you will broaden your horizons by working with different medical, dental, nursing and allied health professionals.

Let us face this future challenge together. In the coming Chinese year of the Monkey, let us learn from the Monkey to be clever, energetic, ambitious and creative with excellent adaptation and curiosity.

On behalf of the federation, I wish all of you success in your career and happiness in your family in the coming Chinese year of the Monkey.

PRINCESS CRUISES
come back new

Explore Alaska's greatest glaciers and most beautiful scenery onboard!

Video for "North to Alaska"

NORTH TO ALASKA

#1 CRUISE LINE IN ALASKA*
TRAVEL WEEKLY
8 STRAIGHT YEARS

Glacier Bay National Park is one of the **"7 Cruise Wonders of the World"** identified by Condé Nast Traveler!

7 Days Voyage of the Glacier

Sail between Vancouver and Anchorage (Whittier)
Island Princess | Coral Princess | Star Princess
Sail between May and Sep 2016

Visiting ports:
Ketchikan, Alaska | Juneau, Alaska | Skagway, Alaska | Glacier Bay National Park, Alaska (Scenic Cruising) | College Fjord, Alaska (Scenic Cruising) / Hubbard Glacier, Alaska (Scenic Cruising)

HKD5,842up

Taxes, Fees & Port Expenses approx: HKD1,443

7 Days Inside Passage

Roundtrip from Seattle or Vancouver
Crown Princess | Star Princess | Ruby Princess
Sail between May and Sep 2016

Visiting ports:
Ketchikan, Alaska | Glacier Bay National Park, Alaska (Scenic Cruising) / Tracy Arm Fjord, Alaska (Scenic Cruising) | Juneau, Alaska | Skagway, Alaska / Sitka, Alaska | Victoria, British Columbia

HKD5,491up

Taxes, Fees & Port Expenses approx: HKD1,638

PRINCESS CRUISES
come back new

2952 8079
www.princess.com

Suite 1207, Tower 1, The Gateway, Harbour City
25 Canton Road, Kowloon, Hong Kong

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Editorial

Prof Bernard MY Cheung

PhD, FRCP, FHKCP, FHKAM(Medicine)
Sun Chieh Yeh Heart Foundation Professor in Cardiovascular Therapeutics
Chief, Division of Clinical Pharmacology
Department of Medicine, University of Hong Kong

Editor

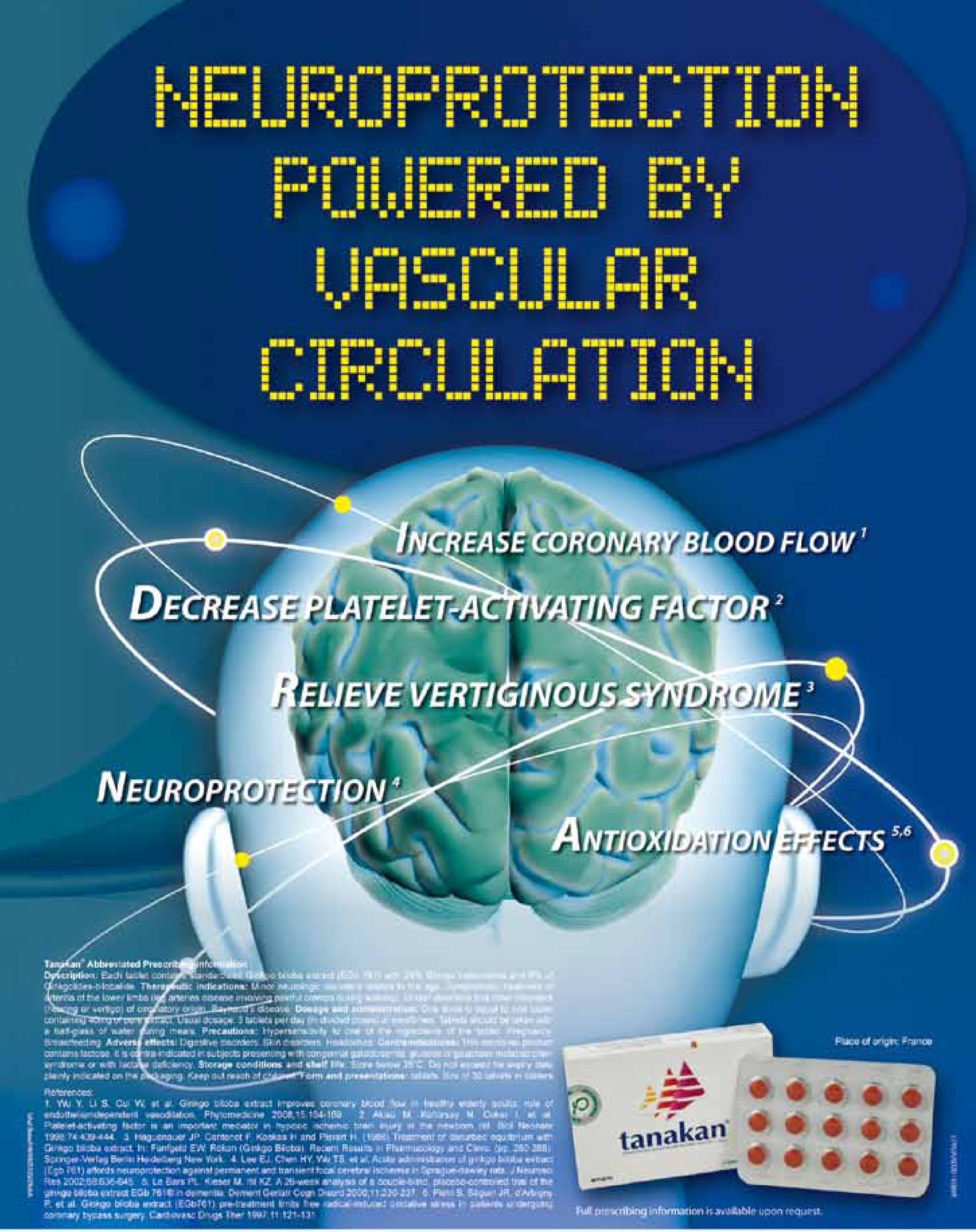
Prof Bernard MY Cheung

This is something of a debut for clinical pharmacology after two decades of the Medical Diary. But what a debut! In this issue, I believe we have a good mix of articles demonstrating the wide scope of clinical pharmacology and therapeutics, and their relevance to every branch of Medicine. In my article, I try to define what clinical pharmacology is. Dr Desmond Yap, a nephrologist, writes about prescribing drugs in patients with kidney disease, a condition that is increasingly common because of the aging population and the availability of renal replacement therapy. Dr Joanne Chiu, an oncologist, describes the exciting horizons in the treatment of cancer. The availability of new classes of drugs to combat cancer is one of the most exciting developments in pharmacology. Biological drugs used for the treatment of cancer and rheumatic diseases have brought new hopes to patients but their prices can often be prohibitive. Dr Tommy Cheung discusses the pros and cons of cheaper biosimilars when the patents of the original biologics expire. For diabetes, the launch of the SGLT2 inhibitors represents a new landmark. This novel class of drugs controls not only diabetes but helps with weight, lipids and blood pressure management. This sounds almost like the polypill! Dr Paul Lee, an endocrinologist, takes us through the promises as well as the pitfalls. In the eyes of the law, drugs are poisons. Professor Cyrus Kumana writes about the constant need to balance risk and benefit in pharmacotherapy. Dr Patrick Leung and Dr Matthew Tsui, two emergency physicians and toxicology experts, give very practical advice and guidance on the interpretation of toxicology tests often encountered in clinical practice.

This bumper issue on clinical pharmacology would not have been possible without the dedicated support of Miss Bianca Lee and her colleagues at the Federation, and the generous support of our sponsors.

At the Federation, we are very saddened by the recent death of Dr Hung Kwan Ngai, who has previously served on the Executive Committee. We were colleagues at Queen Mary Hospital. In the obituary, Dr Dawson Fong recounts his immense contribution to neurosurgery in Hong Kong.

This issue coincides with the start of the Year of the Monkey. A new year brings new hopes and heals old wounds. May I wish our readers a very happy and prosperous Chinese New Year!



What is Clinical Pharmacology?

Prof Bernard MY Cheung

PhD, FRCP, FHKCP, FHKAM(Medicine)
Sun Chieh Yeh Heart Foundation Professor in Cardiovascular Therapeutics
Chief, Division of Clinical Pharmacology
Department of Medicine, University of Hong Kong

Prof Bernard MY Cheung

The most frequent question I get asked by doctors and laymen alike is 'What do clinical pharmacologists do?' It is a common misconception that clinical pharmacologists are clinical pharmacists with special knowledge in pharmacology. This is not altogether wrong because in the United States, many clinical pharmacologists are indeed exactly that. In Hong Kong, China, Australia and Europe however, clinical pharmacologists are usually medical doctors with a special interest in the use of drugs.[1] Although all registered medical practitioners are entitled to prescribe, it is usually in the context of prevention or treatment of disease conditions. Within a particular specialty, there are no better persons with experience in prescribing drugs related to a given specialty than the relevant specialists. A psychiatrist, for instance, does not need to consult anyone on the drugs he or she prescribes every day. Nonetheless there is more to the clinical use of drugs than prescribing to patients in one's own specialty. Clinical pharmacologists are concerned with the full spectrum of drugs for human use, from the development of new drugs, to the testing of drugs in clinical trials, to the monitoring of the use of drugs after they have been marketed, to the detection of adverse effects, toxicity and interactions.[2, 3] Selecting the most appropriate drugs in terms of risk-benefit and cost-benefit, and developing guidelines, also constitute the work of a clinical pharmacologist. Increasingly, genetic and genomic analysis are also used to predict which patients will experience therapeutic benefit or adverse effects. Moreover, clinical pharmacologists treat not only individual patients but also deal with the effectiveness and safety of drugs on a population level.

Why is there a need for clinical pharmacology? It has already been said that drug prescribing forms only one aspect of the clinical use of drugs. The clinical pharmacologist contributes to the effective and safe use of medication in many other ways. Information about drugs is strongly influenced by the pharmaceutical industry, from the types of clinical trials performed, to the dissemination of drug information, the organisation of medical meetings and advertisements in medical journals. This is counterbalanced by the package insert, which is not always carefully read by doctors, and the occasional press releases and letters to health professionals from drug regulatory authorities. The balance is uneven. Clinical pharmacologists therefore play an important role in the provision of advice about the effectiveness and safety of medications. The objectivity, which is necessary in therapeutic decisions that have to weigh up costs, benefits and risks, comes from being a practicing clinician but not necessarily the physician primarily responsible for the patient. The much admired National Institute of Clinical Excellence (NICE) and similar appraisal bodies were set up by clinical pharmacologists. NICE created a stir by putting less weight on expert opinion and more weight on clinical trial evidence and the systematic review (meta-analysis) of the evidence. Critical analysis is needed to question whether the newest drugs are genuinely the most efficacious. Even if evidence supports their superior efficacy, their higher cost means that pharmacoeconomic evaluation becomes necessary to ensure an optimum balance of costs and benefits. Clinical pharmacologists therefore contribute to policy at a local and international level, in areas such as licensing, formularies and prescribing guidelines (Table).

Roles of clinical pharmacology[1]

- As laboratory researchers, clinical pharmacologists rank with other basic scientists as contributors to drug discovery and development.
- As reviewers and interpreters of data about medicines they stand beside epidemiologists and statisticians as contributors to drug development and understanding of drug action.
- As clinicians they teach their students, inform and advise their colleagues, and complement the activities of their colleagues in other clinical specialties as contributors to practical drug therapy.
- As policy makers they complement the contributions of their colleagues in all fields related to the use of medicines.

Can the job be done by pharmacists? The job can be done by pharmacists who have relevant training and experience,[4, 5] just as a pharmacist with relevant training and experience can be very effective in an anticoagulant clinic. Nonetheless a general training in pharmacy does not prepare the pharmacist to undertake the roles of a clinical pharmacologist. The best model is arguably a multidisciplinary one in which clinical pharmacologists and pharmacists work closely together.

Many clinical pharmacologists are appointed by universities and medical schools, and have clinical duties in affiliated hospitals. Universities recognise the importance of clinical pharmacology in the undergraduate medical curriculum, to train future doctors in the rational, appropriate and safe use of drugs. In the UK, this is now taken seriously and forms a crucial part of the training of the medical undergraduate and the intern.[6, 7] The examination of prescribing skills has evolved in recent years to be more like a car driving test with emphasis on competence and safety. Clinical pharmacology is the only clinical specialty that incorporates a significant amount of research training in its postgraduate training programme. Training in clinical trials is a compulsory element.

Apart from the undergraduate medical curriculum, clinical pharmacology is also included as part of the training of other health professionals, such as pharmacists. Pharmacy students benefit from insight into how therapeutic decisions are made in the clinical setting. Indeed, clinical pharmacology may serve as

a bridge and crossroad between the disciplines of Medicine and Pharmacy.

A decade or two ago, the practice of medicine became more evidence based. Large randomized controlled trials and meta-analyses of these trials form the backbone of the evidence base for clinical practice. In the past, many drugs were approved on the basis of good basic science and animal data that demonstrated their mechanisms and biological effects, coupled with small clinical trials that demonstrated safety in small numbers of humans and efficacy based on a surrogate endpoint (such as blood glucose or HDL). In retrospect, the shortcomings of this approach seem obvious. With the emphasis on clinical endpoints, clinical pharmacology comes to the fore as the discipline underpinning the approval of new drugs.[8] Despite this, clinical trials do not necessarily reflect real world clinical practice, and do not have the power to detect rare adverse effects. There is thus a need to study drug use in clinical practice, the realm of pharmacoepidemiology. Rare adverse drug effects are detected via the discipline of pharmacovigilance. The information gained from these studies is as important as the evidence base from clinical trials.

While the reporting of clinical trials tends to promote benefits, such as small gains in progression-free survival that are statistically significant but clinically insignificant, adverse effects can appear to be down played when presented as a long list. Indeed, pharmaceutical companies have a natural tendency to highlight the efficacy of drugs whilst sweeping drug toxicity under the carpet as much as they are allowed to. The occurrence of adverse drug effects is a major reason for medical consultations and admissions, yet drug toxicity and drug-drug interactions are neglected areas in a world that is fixated on blood tests and scans. There is an urgent need to address this hiatus. Fortunately, there is now a better pharmacokinetic understanding of drug metabolism and elimination. The integration of pharamcogenetics and pharmacogenomics into the understanding of why particular patients develop drug toxicity is the way forward.

There are also two key concepts in clinical pharmacology that are commonly misunderstood or overlooked by both the general public and the medical profession. The first is dose-response. The effect of a drug is usually dose-dependent. This means that the drug effect has to be discussed in relation to the dose. Statements like drug A is more efficacious than drug B without reference to the dose-response curve are often meaningless and may even be misleading. Secondly, the fact that all drugs are poisonous is something the public, patients, doctors, and pharmaceutical industry conveniently forget. The public demands 100% safety and zero adverse effects, whilst industry and sometimes doctors pretend to deliver it. The reality is that therapeutic decisions must always balance the risks and benefits. Clinical pharmacologists have the responsibility to speak up and inform when these concepts are overlooked.

The concept that drugs are harmful until proven otherwise can, and should, be extended to traditional, herbal and alternative medicines. The techniques originally developed to evaluate western medicines, such as the randomised double-blind controlled trial, meta-analysis, pharmacovigilance and pharmacoeconomics, can be applied to the evaluation of non-western medicines and nonpharmacological treatments. Such an evaluation is particularly important when there are firm beliefs about the efficacy and safety of the treatment.

An unintended consequence of the pursuit of large clinical trials has been the escalating expense of developing a new drug. Large phase 3 trials are extremely expensive. Thus it has recently been appreciated that finite financial resources are better spent on properly conducted phase 1 trials, so that decisions on the further development of new drugs can be made earlier, before proceeding to the expensive phase 3 trials. As a consequence, phase 1 clinical trials centres have sprung up all over the world. In Hong Kong, there are two dedicated phase 1 clinical trials centres, one each at the Prince of Wales Hospital and Queen Mary Hospital. These purpose built units are equipped and staffed to conduct first-in-man trials in patients and normal volunteers. Careful observations in such specialised facilities enable new drugs to be more fully characterized and studied before they are tested in large multicentre trials.

Although the subject is immensely important from the public's point of view, there is a worldwide shortage of clinical pharmacologists. Young graduates may not be attracted to the subspecialty because it does not usually lead to a career in private practice. In addition, hospitals may want more front line clinicians, especially in procedure-based specialties. Yet, from the point of view of a health system, such as the Hong Kong Hospital Authority, it pays to improve the effectiveness, safety and appropriate use of medications. The money saved, the harm prevented and the appropriate treatment of patients will pay for the employment of clinical pharmacologists many times over.

There are already chips that can analyse DNA variants for susceptibility to not only disease but response (beneficial or adverse) to drugs. It is not difficult to imagine that this could become the standard of care in advanced countries, and future prescribing would have to take account of such information.[9] As the interpretation of these results and how they affect drug prescribing is specialised, the clinical pharmacologist is likely to have an input, much as a radiologist is consulted over X-rays and scans or the microbiologist over the choice of antibiotics.

In conclusion, clinical pharmacology is the scientific study of drugs for human use. It is a vast field and includes the development of drugs, clinical trials, pharmacokinetics, drug toxicity, evaluation of drug efficacy, safety and cost-effectiveness, adverse drug reactions, pharmacovigilance, studies of drug utilisation, clinical guidelines on drug therapy, pharmacogenetics and pharmacogenomics. It is an unconventional subspecialty within Medicine and makes an unusually important contribution to the safe and effective use of medications in man.

References

1. Aronson JK. A manifesto for clinical pharmacology from principles to practice. Br J Clin Pharmacol. 2010 Jul;70(1):3-13.
2. Birkett D, Brøsen K, Cascorbi I, Gustafsson LL, Maxwell S, Rago L, Rawlins M, Reidenberg M, Sjöqvist F, Smith T, Thuerman P, Walubo A, Orme M, Sjöqvist F. Clinical pharmacology in research, teaching and health care: Considerations by IUPHAR, the International Union of Basic and Clinical Pharmacology. Basic Clin Pharmacol Toxicol. 2010 Jul;107(1):531-59.
3. Dollery CT. Clinical pharmacology – the first 75 years and a view of the future. Br J Clin Pharmacol 2006: 61: 650-65.
4. Somogyi A, Loke YK, Ferro A, Lewis LD, Cohen AF, Ritter JM. Clinical pharmacology: a declaration of intent. Br J Clin Pharmacol. 2010 Jul;70(1):1-2.
5. Tucker GT, Miners JO. What's in a name? Br J Clin Pharmacol. 2011 May;71(5):785-6
6. Webb DJ. The roles of clinical pharmacologists in UK universities. Br J Clin Pharmacol. 2012 Jun;73(6):874-7.
7. O'Shaughnessy L, Haq I, Maxwell S, Llewelyn M. Teaching of clinical pharmacology and therapeutics in UK medical schools: current status in 2009. Br J Clin Pharmacol. 2010 Jul;70(1):143-8.
8. Aronson JK, Cohen A, Lewis LD. Clinical pharmacology - providing tools and expertise for translational medicine. Br J Clin Pharmacol. 2008 Feb;65(2):154-7.
9. Ritter JM. 1974-2014: Reflections on the evolution of clinical pharmacology in the past 40 years and a message to our readers. Br J Clin Pharmacol. 2014;Jan;77(1):1-4.

Drugs Prescription in Patients with Kidney Disease

Dr Desmond YH YAP

MBBS (HK), MD (HK), MRCP (UK), FHKCP, FHKAM, FRCP (Edin, Glasg)

Clinical Assistant Professor, Division of Nephrology, Department of Medicine, The University of Hong Kong

Dr Desmond YH YAP

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 29 February 2016.

Introduction

Chronic kidney disease (CKD) is a common and important clinical entity with a growing prevalence in different populations[1]. The kidneys are vital organs that are responsible for the maintenance of fluid and electrolyte balance, production of hormones (e.g. erythropoietin, active vitamin D), control of blood pressure, elimination of uremic toxins and the metabolism of drugs. Not surprisingly polypharmacy is common in patients with CKD. Patients with kidney dysfunction may thus be prone to substantial problems in drug metabolism and interaction, and are also more susceptible to the nephrotoxic effects of drugs. This review highlights the issues regarding drug prescription in patients with kidney dysfunction.

Effect of renal impairment on drug absorption, distribution and elimination

CKD patients are often prescribed phosphate-binders and proton pump inhibitors, both of which can affect the absorption of other acidic drugs. In patients with significant uremia, nausea and repeated vomiting can significantly reduce absorption of oral medications. In patients with nephrotic syndrome, decreased serum albumin can influence distribution of drugs that are highly protein-bound. One example of such is furosemide: a much higher dose might be required to achieve diuresis in patients who are markedly nephrotic[2]. Warfarin, which is also highly protein-bound, can produce substantial fluctuations in the clotting profile of patients with significant proteinuria, and hence close monitoring of the International Normalized Ratio (INR) is advisable[3]. Most drugs will undergo oxidation/reduction or hydrolysis before their excretion. These metabolic mechanisms may be impaired in patients with renal failure. Elimination of drugs and their metabolites are also decreased in patients with a reduced glomerular filtration rate (GFR). Drug elimination is particularly difficult in those on dialysis. In hemodialysis patients, the elimination of drugs is dependent on the pore size of the filter as well as blood and dialysate flow rate during hemodialysis[4]. In peritoneal dialysis, elimination of drugs is generally poor although those with small molecular size and high volume of distribution may have better clearance during peritoneal dialysis[5]. Drugs that are highly protein-bound might also have enhanced clearance due to protein loss in the peritoneal effluent[5].

Table 1. Commonly used methods to estimate renal function and glomerular filtration rate.

Methods	Formula	Remarks
Serum creatinine (Cr) level	N/A	• Insensitive, becomes abnormal only when GFR is decrease halved • Problematic in patients with reduced muscle mass or marked peripheral edema • Certain drugs can affect tubular handling of Cr or interfere with Cr assays
Cockcroft-Gault equation	CrCl (mL/min) = [(140-Age) x lean BW (kg)] ÷ [Serum Cr (mg/dL) x 72] x 0.85 (if female)	• Easy and convenient to use • Satisfactory performance in patients with stable renal function • Problematic in patients with changing clinical condition or renal function
MDRD equation (Chinese validated equation)	GFR (mL/min/1.73m2) = 175 $x(SCr)^{-1.234}$ x $(Age)^{-0.179}$ x (0.79 if female)	• Equation validated in Chinese population • Accurate in patients with moderate renal impairment • Less precise in extremes of renal function
CKD-EPI equation	GFR = 141 x min $(SCr/\alpha, 1)^{\alpha}$ x max $(SCr/K, 1)^{-1.209}$ x $0.993^{(Age)}$ x $1.108^{(\text{if female})}$ x 1.159 (if black) K=0.7 if female & 0.9 if male α=-0.329 if female & -0.411 if male Min – The minimum of SCr/K or 1 Max – The maximum of SCr/K or 1 SCr in (mg/dL)	• Better performance than MDRD equation in patients with higher GFR • Not widely adopted in many laboratories

GFR: Glomerular filtration rate; MDRD: Modification of Diet in Renal Disease Study; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration

Dosage adjustment in patients with renal impairment

In general, dosage adjustment is according to the GFR. While serum creatinine (Cr) level is a commonly used biomarker for renal function, its application in certain patient groups can be misleading, for example in an elderly patient with reduced muscle mass or patients who are markedly edematous. Other potential pitfalls of using serum Cr to assess renal function stems from its propensity for drug interference (e.g. cimetidine can inhibit tubular Cr absorption and ascorbic acid can interfere with Cr assay). The Cockcroft-Gault Equation is a widely adopted and convenient way to estimate GFR but is accurate only in patients with stable renal function. Use in patients with changing clinical condition and renal function may thus be difficult. The Modification of Diet in Renal Disease Study (MDRD) equation is gaining popularity for gauging GFR. The MDRD is most accurate in subjects with moderate renal

dysfunction but can be inaccurate at the extremes of kidney function[6,7]. Other methods of GFR measurement include Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation that is also based on the four variables used in the MDRD formula (Table 1). Previous studies report the CKD-EPI equation to show less bias than the MDRD equation in patients with higher GFR[8]. Nonetheless the CKD-EPI equation is still not widely applied in most laboratories. Drugs that depend on significant renal elimination will require dosage adjustment in patients with kidney impairment. This can be achieved by reducing the dose or frequency of administration, depending on the characteristics of the drug. Appropriate dose modification, precautions and monitoring can help minimize the side effects in CKD patients (Table 2). One should also review the clinical indications and consider alternative treatments before prescribing drugs with nephrotoxic potential.

Table 2. Drugs that commonly cause problems in renal failure patients.

Drugs	Possible clinical manifestations in CKD patients
Antimicrobials	
Penicillin, cephalosporins, quinolones	• Confusion, seizure
Vancomycin, aminoglycoside	• Direct nephrotoxicity
Acyclovir	• Confusion, seizure
Amphotericin B	• Renal deterioration, electrolyte imbalance (potassium, magnesium)
Drugs for cardiovascular disease	
ACEI/ARB	• Can precipitate renal deterioration, especially in patients with renal artery stenosis or pre-existing CKD
Digoxin	• Increased risk of digoxin overdose (nausea, vomiting, yellow xanthopsia, arrhythmia) in CKD patients, especially in hypo/hyperkalemia
Drugs for endocrine and metabolic diseases	
Sulphonylurea and DDP-4 inhibitors	• Increased risk of hypoglycemia (sometimes prolonged hypoglycemia)
Metformin	• Severe lactic acidosis
(PPAR-γ) agonists	• Can accentuate fluid overload and heart failure
Allopurinol	• Acute interstitial nephritis • Marrow suppression
Cytotoxic and immunosuppressive drugs	
Cyclophosphamide, methotrexate, mycophenolic acid	• Severe myelosuppression
Calcineurin inhibitors (CNI)	• Enhanced CNI toxicity (hypertension, tremor, acute and chronic nephrotoxicity)
Analgesics	
NSAID & COX-2 inhibitors	• Acute renal failure • Acute and chronic interstitial nephritis • Membranous glomerulopathy
Opioid analgesics	• Drowsiness and respiratory depression in severe renal impairment

ACEI=Angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; COX-2 inhibitors = cyclo-oxygenase inhibitors; DDP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; NSAID = non-steroidal anti-inflammatory drugs; (PPAR-γ) agonists = peroxisome proliferator-activated receptor gamma agonists

Drug-induced nephrotoxicity

Non-steroidal anti-inflammatory drugs (NSAID) can cause acute or chronic renal deterioration, especially in patients with pre-existing kidney dysfunction and hence should be avoided in these patients[9]. Some antimicrobials such as aminoglycosides, vanocymycin, and amphotericin B can induce direct nephrotoxicity[10]. In this context, therapeutic drug monitoring of vancomycin and aminoglycoside levels may help optimize the drug dosage/schedule and avoid the potential nephrotoxic effects. The administration of amphotericin B should be followed by close monitoring of renal function and electrolytes (especially potassium and magnesium levels). The use of ACEI/ARB can precipitate kidney dysfunction, especially in patients with pre-existing renal disease or renal artery stenosis. Clinicians should be alert to any renal bruits before initiation of ACEI/ARB therapy and monitor renal function soon (preferably in 1-2 weeks) after the commencement of such therapy. In general, an increase in serum Cr >15% from baseline may warrant discontinuation of ACEI/ARB. Clinicians should also be alert to hyperkalemia when ACEI/ARB is used in CKD patients. Certain drugs such as the penicillins, rifampicin, allopurinol and proton-pump inhibitors can cause renal dysfunction due to acute or chronic interstitial nephritis.

Drug-drug interaction in patients with renal disease

Patients who suffer from immune-mediated glomerulonephritis or who have undergone kidney transplantation require long-term immunosuppressive treatment, commonly with calcineurin inhibitors (CNI) such as cyclosporine or tacrolimus. CNIs are associated with acute and chronic nephrotoxicity, and some antimicrobials may cause drug-drug interactions by influencing the cytochrome P450 system[11]. In this context, rifampicin can enhance CNI metabolism whereas macrolides or azoles can decrease it. Inappropriate adjustment of CNI dosages in these situations can precipitate kidney allograft rejection or acute CNI toxicity. Azathioprine (AZA) and allopurinol are both common drugs used in patients with immune-mediated glomerular disease or a kidney allograft. Nonetheless the concomitant administration of these two drugs is a lethal combination that can result in severe myelosuppression and hence fulminant sepsis[12]. Patients with glomerulonephritis or a kidney allograft who require allopurinol treatment might need substitution of AZA with mycophenolic acid.

Conclusion

Absorption, distribution and elimination of drugs is altered in patients with renal failure. Nephrotoxic effects of drugs can be accentuated in patients with pre-existing kidney dysfunction. Careful consideration of clinical indications and alternatives, appropriate dosage adjustment and close monitoring of renal function and electrolytes should be exercised in patients with CKD.

References

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038-47.
2. Kodner C. Nephrotic syndrome in adults: diagnosis and management. Am Fam Physician 2009;80:1129-34.
3. Ganeval D, Fischer AM, Barre J, et al. Pharmacokinetics of warfarin in the nephrotic syndrome and effect on vitamin K-dependent clotting factors. Clin Nephrol 1986;25:75-80.
4. Lee CS, Marbury TC. Drug therapy in patients undergoing haemodialysis. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1984;9:42-66.
5. Hirata S, Kadowaki D. Appropriate drug dosing in patients receiving peritoneal dialysis. Contrib Nephrol 2012;177:30-7.
6. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
7. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006;17:2937-44.
8. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
9. Bennett WM, Henrich WL, Stoff JS. The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. Am J Kidney Dis 1996;28:S56-62.
10. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. Am Fam Physician 2007;75:1487-96.
11. Immunosuppressive drug interactions with anti-infective agents. Am J Transplant 2004;4 Suppl 10:164-6.
12. Gearry RB, Day AS, Barclay ML, Leong RW, Sparrow MP. Azathioprine and allopurinol: A two-edged interaction. J Gastroenterol Hepatol 2010;25:653-5.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Drugs Prescription in Patients with Kidney Disease" by Dr Desmond YH YAP and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 29 February 2016. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **A much higher dose of furosemide is required to achieve satisfactory diuresis in patients with marked nephrotic syndrome.**
2. **The dosage of acyclovir should be appropriately reduced in elderly patients with renal impairment.**
3. **The use of PPAR-γ agonists in patients with chronic kidney disease will not precipitate fluid overload and heart failure.**
4. **The use of metformin in patients with moderate to severe renal dysfunction can lead to severe lactic acidosis.**
5. **The administration of rifampicin in kidney transplant recipients can significantly increase the drug level of calcineurin inhibitors.**
6. **The concomitant use of allopurinol and azathioprine can lead to severe myelosuppression.**
7. **The use of ACEI/ARB in patients with chronic kidney disease can aggravate hypokalemia.**
8. **Aminoglycoside should be avoided in patients with pre-existing renal impairment.**
9. **The use of COX2 inhibitors will not lead to renal deterioration in patients with chronic renal impairment.**
10. **The Modification of Diet in Renal Disease (MDRD) equation is most accurate for estimation of glomerular filtration rate at extremes of renal function.**

ANSWER SHEET FOR FEBRUARY 2016

Please return the completed answer sheet to the Federation Secretariat on or before 29 February 2016 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Drugs Prescription in Patients with Kidney Disease

Dr Desmond YH YAP

MBBS (HK), MD (HK), MRCP (UK), FHKCP, FHKAM, FRCP (Edin, Glasg)

Clinical Assistant Professor, Division of Nephrology, Department of Medicine, The University of Hong Kong

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to January 2016 Issue

Psychiatric Care for Chronic Pain Patients – An Update

1. F 2. F 3. T 4. F 5. T 6. T 7. F 8. F 9. T 10. F

New Treatments and Hopes for Cancer Patients

Dr Joanne WY CHIU

FHKAM (Medicine), FHKCP (Med Onc), MBBS (HK), MRCP (UK), B.Sc. (Canada), M.Sc. (Canada)

Clinical Assistant Professor, Division of Hematology and Medical Oncology
Deputy Medial Director, Phase 1 Clinical Trials Centre
Department of Medicine, LKS Faculty of Medicine

Dr Joanne WY CHIU

Cancer is one of the most important causes of death in the modern world, taking more than 8 million lives each year. For a solid tumor, the principle of cure has been surgical removal of the tumor mass or, occasionally, local ablative therapy. When cancer cells spread beyond the local region, the aim of treatment becomes long-term control of tumor growth with drug treatment. It is often a marathon consisting of a series of continuous treatments until the last day of life.

Cancer is a disease in which cells continue to grow uncontrollably, invading healthy tissue in the body. The traditional drug treatment, chemotherapy, attacks cells that are in the process of rapid cell division. It damages fast growing cancer cells, but also affects normal cells that undergo rapid physiological turnover. The development of chemotherapy dates back to the early 20th century when animal models of cancer were used for drug screening. Progress was nonetheless hindered by a lack of knowledge and experience in the performance of clinical trials to test potentially toxic compounds in humans. Research on vesicant war gases during World War II led to the observation that mustards could suppress cell growth of bone marrow in humans, and provided the foundation for the earliest treatment of hematological malignancy. During the post-war period, many institutions started clinical research in chemotherapy, and the first chemotherapy for a solid tumor, 5-fluorouracil, was introduced to the clinical environment in 1958[1]. The later part of the 20th century marked the blooming of new chemotherapy. Yet, the non-specific action of these drugs and their associated toxicities prompted the need for better treatments. There was also concern about the lack of a biomarker to guide responsiveness to chemotherapy. The chance of a positive response to chemotherapy varies, from over 50% in certain cancers for first line treatment, to less than 10% in others or in refractory cases. Many patients suffer much discomfort and toxicity from chemotherapy before they experience any benefit.

With advances in technology and the ability to study tumor cells at the sub-cellular level, it has become apparent that cancer cells carry erroneous genetic material or over-express signaling proteins that drive tumor growth. Development of molecules to interfere with these specific signals began in the 1980's and the number of targeted therapies has escalated since then. Today there are more than 60 targeted therapies that are approved by the U.S. Food and Drug Administration for treatment of cancer, and the number continues to grow. Targeted therapy can be used alone, or in conjunction with chemotherapy to improve overall efficacy. The more specific nature of targeted therapy has also revolutionized the process of drug development. Instead of giving random cancer patients a new drug with the hope that it might work, clinical trials of targeted therapy now often pre-select patients according to a disease type that has an expected molecular aberration, or pre-screen patients at recruitment for the molecular subtypes of interest[2-4]. In carefully selected patients with the right molecular type, the response rate to treatment can be markedly raised. The remarkable efficacy observed in early phase studies has expedited approval for a number of targeted therapies. The time from bench-top research to clinical application can in some cases be shortened from over 10 years to 4 or 5 years. Examples of drugs that have received early approval due to an exceptional response include crizotinib for ALK-mutated lung cancer[5], pertuzumab for HER2-positive breast cancer[6], and palbociclib for hormonal-receptor positive breast cancer[7].

While an increasing capability to study genetic material and breakthroughs in targeted therapy continue to shape treatment algorithms, the unexpected extraordinary efficacy of immunotherapy has aroused further optimism. Melanoma is an aggressive skin cancer that responds poorly to treatment. Early phase clinical trials 10 years ago reported dramatic shrinkage of tumor in some terminal melanoma patients prescribed a class of immunotherapy called CTLA-4 inhibitor[8]. This drug aims to resume the function of the immune system in clearing tumor cells. To the surprise of researchers, the tumor remained under control in responding patients, even after treatment was stopped. Some patients remained in long-term disease remission and required no further cancer treatment. Although the application of this drug is limited by its high cost and toxicities, we now know that even advanced stage cancer is potentially curable if the key to switch on our own immune surveillance system can be found. Another class of better-tolerated immunotherapy, anti-PD1 antibody, has just been formally launched in Hong Kong in December 2015. Today, the clinical application of immunotherapy has been extended to lung cancer[9-11] and kidney cancer[12].

Many targeted therapies and immunotherapies are being actively studied in Hong Kong. The Phase 1 Clinical Trials Center is a special facility dedicated to conduction of early phase clinical trials with stringent safety monitoring. Cancer treatment is a rapidly evolving field. By participating in scientific studies, we offer our patients the opportunity to experience novel cancer treatments and benefit from them. We encourage

patients to seek more options even at the initial stage of treatment, as many new treatments are most effective and offer best survival benefit when used early.

References

1. Curreri AR, Ansfield FJ, Mc IF, Waisman HA, Heidelberger C (1958) Clinical studies with 5-fluorouracil. Cancer research 18 (4):478-484
2. Kim ES, Herbst RS, Wistuba, II, Lee JJ, Blumenschein GR, Jr., Tsao A, Stewart DJ, Hicks ME, Erasmus J, Jr., Gupta S, Alden CM, Liu S, Tang X, Khuri FR, Tran HT, Johnson BE, Heymach JV, Mao L, Fossella F, Kies MS, Papadimitrakopoulou V, Davis SE, Lippman SM, Hong WK (2011) The BATTLE trial: personalizing therapy for lung cancer. Cancer discovery 1 (1):44-53. doi:10.1158/2159-8274.CD-10-0010
3. Rubin EH, Gilliland DG (2012) Drug development and clinical trials--the path to an approved cancer drug. Nature reviews Clinical oncology 9 (4):215-222. doi:10.1038/nrclinonc.2012.22
4. Abrams J, Conley B, Mooney M, Zwiebel J, Chen A, Welch JJ, Takebe N, Malik S, McShane L, Korn E, Williams M, Staudt L, Doroshow J (2014) National Cancer Institute's Precision Medicine Initiatives for the new National Clinical Trials Network. American Society of Clinical Oncology educational book / ASCO American Society of Clinical Oncology Meeting:71-76. doi:10.14694/EdBook_AM.2014.34.71
5. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, Riely GJ, Solomon B, Ou SH, Kim DW, Salgia R, Fidias P, Engelman JA, Gandhi L, Janne PA, Costa DB, Shapiro GI, Lorusso P, Ruffner K, Stephenson P, Tang Y, Wilner K, Clark JW, Shaw AT (2012) Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. The Lancet Oncology 13 (10):1011-1019. doi:10.1016/S1470-2045(12)70344-3
6. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagussa P (2012) Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. The Lancet Oncology 13 (1):25-32. doi:10.1016/S1470-2045(11)70336-9
7. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M, Shparyk Y, Thummala AR, Voytko NL, Fowst C, Huang X, Kim ST, Randolph S, Slamon DJ (2015) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. The Lancet Oncology 16 (1):25-35. doi:10.1016/S1470-2045(14)71159-3
8. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ (2010) Improved survival with ipilimumab in patients with metastatic melanoma. The New England journal of medicine 363 (8):711-723. doi:10.1056/NEJMoa1003466
9. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. The New England journal of medicine 373 (2):123-135. doi:10.1056/NEJMoa1504627
10. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crino L, Blumenschein GR, Jr., Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. The New England journal of medicine 373 (17):1627-1639. doi:10.1056/NEJMoa1507643
11. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. The New England journal of medicine 372 (21):2018-2028. doi:10.1056/NEJMoa1501824
12. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P (2015) Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. The New England journal of medicine 373 (19):1803-1813. doi:10.1056/NEJMoa1510665

NOW APPROVED

FOR PATIENTS LIKE JANE

JARDIANCE PROVIDES A POSITIVE EXPERIENCE

CV: cardiovascular; SGLT-2: sodium glucose cotransporter 2

* JARDIANCE is not indicated for weight loss

† Weight change was a secondary endpoint in clinical trials

References:

1. Jardiance® Hong Kong prescribing information. **2.** Merker L, et al. Poster 1079-P. Presented at the 74th Scientific Session of American Diabetes Association, 13-17 June 2014, San Francisco, CA, USA. **3.** Roden M, et al. Lancet Diabetes Endocrinol. 2013;1:208-219. **4.** Häring HU, et al. Diabetes Care. 2014;37:1650-1659. **5.** Häring HU, et al. Diabetes Care. 2013;36:3396-3404. **6.** Rosenstock J, et al. Diabetes Obes Metab. 2015;17:936-948. **7.** Zinman B, et al. N Engl J Med. 2015 Sep 17. [Epub ahead of print].

JARDIANCE®

Presentation: Empagliflozin. Film-coated tablet 10 mg and 25 mg. **Indications:** Adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as monotherapy or as combination therapy with other glucose-lowing medicinal products including insulin. **Dosage and administration:** Recommended starting dose is 10 mg once daily. For patients who tolerate 10 mg and need additional glycaemic control, their dose can be increased to 25 mg once daily. Can be taken with or without food. **Contraindication:** Hypersensitivity to empagliflozin or to any of the excipients. **Special warnings and precautions:** Should not be used in patients with type 1 diabetes or diabetic ketoacidosis. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 or CrCl <60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl persistently below 45 ml/min. Should not be initiated in patients with eGFR below 60 ml/min/1.73 m^2 or CrCl <60 ml/min; ESRD or patients with dialysis; aged 85 years and older; severe hepatic impairment. Caution should be exercised in patients at risk for volume depletion. Temporary interruption of treatment until the fluid loss is corrected or in patients with complicated urinary tract infections. Caution in patients with NYHA III and IV cardiac failure. Avoid use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. A lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia when used in combination with empagliflozin. Test positive for glucose in urine. Should be avoided during pregnancy; breast-feeding. Caution when driving or operating machines. **Interactions:** Diuretics, insulin & insulin secretagogues. May decrease efficacy with inducers of UGT enzymes. **Adverse reactions: Very common:** hypoglycaemia when used with sulphonylurea or insulin. **Common:** vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection, pruritus (generalised), increased urination. **Uncommon:** volume depletion, dysuria. **Note:** Before prescribing, please consult full prescribing information.

Boehringer Ingelheim

Boehringer Ingelheim (HK) Ltd.
1504-9, Great Eagle Centre, 23 Harbour Road, Wanchai, Hong Kong
Tel: (852) 2596 0033 Fax: (852) 2827 0162 www.boehringer-ingelheim.com

JAR-10-2015-02

2015 - A Year of SGLT2 Inhibitors in Hong Kong

Dr Paul Chi-Ho LEE

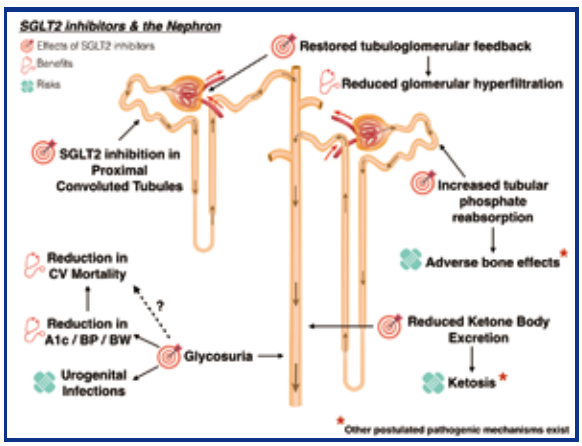
MBBS (HK), MRCP (UK), FHKCP (Endocrinology), FHKAM (Medicine)
Clinical Assistant Professor, the University of Hong Kong

2015 marks a significant year for type 2 diabetic patients in Hong Kong. With the launch of Dapagliflozin at the beginning of the year, followed by Canagliflozin and Empagliflozin towards year-end, this new class of oral anti-diabetic agent, sodium-glucose cotransporter 2 (SGLT2) inhibitors, has brought new hope for patients with type 2 diabetes mellitus (T2DM).

SGLT2 inhibitors introduce a novel, insulin independent approach to glycaemic control in T2DM. Inhibition of SGLT2, whose renal expression is paradoxically upregulated in T2DM, reduces glucose reabsorption in the proximal convoluted tubules and thereby increases glycosuria and alleviates hyperglycaemia. Various randomized controlled trials have demonstrated their clinical efficacy both as monotherapy and as add-on therapy.[1,2] In general, SGLT2 inhibitors lower glycated hemoglobin (HbA1c) by 0.5 to 1% and fasting glucose by around 1 mmol/L compared with placebo. As one of the approved second anti-diabetic agents after metformin, SGLT2 inhibitor is an attractive option given its metabolic effects beyond improved glycaemic control. In contrast to most commonly used glucose lowering drugs that cause weight gain or are at most weight-neutral, SGLT2 inhibitors promote weight loss of 2-3 kg over 6-12 months. Moreover, they improve blood pressure through osmotic diuresis, with a small reduction in systolic blood pressure by around 4mmHg and diastolic blood pressure by around 2mmHg.[1,2]

With the increasing use of SGLT2 inhibitors globally, some safety issues undetected during drug development have gradually emerged. In mid-2015, the Food and Drug Administration (FDA) issued a warning about the increased risk of diabetic ketoacidosis related to their use.[3] Several plausible mechanisms were postulated to explain this association: in those on background insulin therapy in whom insulin dose was reduced in order to minimize the risk of hypoglycaemia during concomitant use of a SGLT2 inhibitors, there could be increased lipolysis and hepatic ketogenesis.[4] Even among patients not prescribed insulin therapy, SGLT2 inhibition could increase the reabsorption of ketone bodies and thereby decrease their renal clearance.[4] Due to the expression of SGLT2 on pancreatic α cells, SGLT2 inhibitors could increase glucagon secretion.[4] Although the overall risk is low, prescribing physicians should be fully aware of this potential complication related to SGLT2 inhibition, as well as a few common triggers for this adverse event that include reductions in insulin dose, intercurrent illness, dehydration, low caloric intake and prescription during a peri-operative period.[5] Notably, since SGLT2 inhibitors can decrease the renal clearance of ketone bodies, physicians should also be cautious about the potential limitation of utilizing the presence of urine ketones to screen for ketosis, as a false negative result could delay proper management of life-threatening diabetic ketoacidosis.[4]

In September 2015, the FDA strengthened the warning about another uncommon side effect: an imbalance in bone fracture incidence with the use of an SGLT2 inhibitor, Canagliflozin.[6] Canagliflozin may reduce bone mineral density at both the hip and spine, and fractures can occur as early as 12 weeks following initiation of therapy.[6] Increased parathyroid hormone level and/or decreased 1,25-dihydroxyvitamin D level related to SGLT2 inhibition were proposed pathogenic mechanisms.[7]



Nephron image copyright from Alila Medical Media, used under license from Shutterstock.com

Towards the end of 2015, the EMPA-REG Outcome study presented the first positive cardiovascular (CV) outcome trial that involved more than 7,000 type 2 diabetic patients with established CV disease. In this placebo-controlled study, not only did empagliflozin reach the primary endpoint in reducing the composite outcome of CV death, non-fatal myocardial infarction, or nonfatal stroke, empagliflozin was also shown to produce a 38% relative risk reduction in CV mortality. Notably, the events of CV deaths between empagliflozin and placebo diverged as early as less than 6 months after the study started.[8] Given the osmotic diuretic effects of SGLT2 inhibitors, it has been questioned whether the reduced CV mortality could be attributed mostly to the significant reduction in heart failure-related hospitalization. Nonetheless until the results

of CV outcome trials of other SGLT2 inhibitors are available, it remains to be seen whether this CV benefit is a class effect or a compound specific outcome.

Finally, the preliminary renal data from the EMPA-REG Outcome study, presented during American Society of Nephrology Renal Week 2015, closed the year by demonstrating that empagliflozin also significantly reduced the composite renal endpoint, which included doubling of serum creatinine, end-stage renal disease or renal death, among study patients with an estimated glomerular filtration rate less than 60ml/min. It has been suggested that SGLT2 inhibition may confer renal protection in diabetic nephropathy, in addition to the conventional renin-angiotensin-aldosterone system blockade. In experimental models, through tubulo-glomerular feedback, SGLT2 inhibition led to an increase in distal sodium delivery, with a consequent increase in adenosine-mediated afferent arteriolar vasoconstriction, decrease in glomerular hyperinfiltration and thus attenuation of renal injury.[9]

Time flies and one year has passed. As a novel oral hypoglycaemic agent in Hong Kong, more long-term data regarding safety and clinical efficacy of SGLT2 inhibitors are eagerly awaited. Both CV and diabetic kidney disease remain the major causes of morbidity and mortality in the vast majority of type 2 diabetic patients. Given their body weight, blood pressure and glucose lowering effects, together with their published CV and potential renal benefits, albeit their uncommon urogenital side effects and recent FDA warnings, diabetologists remain hopeful that SGLT2 inhibitors will continue to be a durable and useful oral agent in the comprehensive management of T2DM.

References

1. Brunton SA. The potential role of sodium glucose co-transporter 2 inhibitors in the early treatment of type 2 diabetes mellitus. Int J Clin Pract. 2015;69(10):1071-1087.
2. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs. 2015;75(1):33-59.
3. FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood
4. Taylor SI, Blau JE, Rother KI. SGLT2 Inhibitors May Predispose to Ketoacidosis. J Clin Endocrinol Metab. 2015;100(8):2849-2852.
5. Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. Diabetes care. 2015;38(9):1638-1642.
6. FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density.
7. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol. 2015;3(1):8-10.
8. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-2128.
9. Skrtic M, Cherney DZ. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Curr Opin Nephrol Hypertens. 2015;24(1):96-103.

Radiology Quiz

Dr Kenneth KY CHEUNG

Department of Radiology, Queen Mary Hospital.

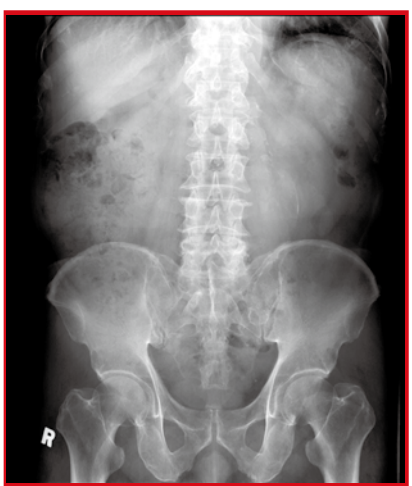


Figure 1: AXR on presentation.

Background:

A 73 year old gentleman with a past history of hypertension and diabetes mellitus presented to his GP with worsening left abdominal pain.

Questions:

1. What are the findings from the AXR? (Figure 1)
2. What is the appropriate management?
3. What further imaging is required for accurate delineation?

(See P.39 for answers)

Use and Interpretation of Toxicology Tests with Clinical Wisdom

Dr LEUNG Siu Chung
MBBS (HK), CME-certified (1 July 2015 to 30 June 2018)
Resident, A&E Department, Queen Mary Hospital

Dr TSUI Sik Hon
FRCP (Edin), FHKAM (Emergency Medicine)
COS, A&E Department, Queen Mary Hospital


Dr LEUNG Siu Chung Dr TSUI Sik Hon

Introduction

Fuelled by the recent concern about lead exposure from drinking water drawn from water boilers and water pipes made from lead-containing welding material, concerns about environmental contamination with toxins and heavy metals have attracted much media attention.[1] Whilst chronic exposure to potentially toxic substances remains a public health if not a political concern, it is only part of the spectrum of clinical toxicology. The acute and chronic effects of substance abuse and harmful use of medicinal products also provoke attendance at emergency departments, methadone clinics, substance abuse clinics, and toxicology clinics in the public sector. With increased service availability, laboratory toxicology tests are becoming increasingly popular in the hospital, out-patient and commercial settings. Nonetheless medical practitioners may face a challenge when confronted by worried patients with seemingly alarming reports, usually issued by commercial toxicology laboratories.

This article will address some of the pitfalls and give advice on the interpretation of toxicology test results.

In contrast to internal medicine that emphasises individualised care for a particular patient, clinical toxicology may be perceived as "external medicine" wherein the adverse effects of an environmental, pharmaceutical, venomous or foreign substance are studied.[2] Nonetheless the approach to patients with suspected poisoning is not dissimilar to that for patients with other medical conditions. Diagnosis of poisoning should be made primarily on a clinical basis with recording of a thorough history of exposure, and elucidation of symptoms and physical signs. Constellations of clinical features constitute toxic syndromes (toxidromes) caused by certain agent classes, and recognition of such is useful to exclude some unrelated causes before ordering further investigations.[3] General tests such as blood glucose measurement, pulse oximetry, electrocardiography, serum electrolytes with or without calculation of anion gap, urine pregnancy test for female patients of reproductive age, and focused quantitative assays will usually suffice in the management of poisoned patients.[4] Ancillary laboratory toxicology tests should be specific to the problems that are clinically suspected. In addition, the clinical rule of "treat the patient, not the numbers" still holds true.

The American College of Medical Toxicology and The American Academy of Clinical Toxicology supported the Choosing Wisely® initiative that endorsed the list of "Ten Things Physicians and Patients Should Question" about clinical toxicology.[5] Heavy metal screening, for example, should not be ordered to assess non-specific symptoms in the absence of known excessive exposure to metal. Exposure to metals in the environment per se does not equate to poisoning. Dose, duration of exposure, and individual susceptibility should be taken into account. Indiscriminate testing often leads to misleading results, and unnecessary fear and therapy when they fall outside the "normal" range.

Beside urine immunoassays

Immunoassay-based urine tests provide the advantages of good bedside accessibility, non-invasive nature of specimen sampling, instantly available results, easily obtainable kits and relatively low cost. Many are equipped with multi-drug panels that enable a number of drugs of abuse to be screened from a single sample by lateral flow chromatography. One example is the Alere ABON™ One-step Multi-drug Tests (Alere Inc., Waltham, Massachusetts, United States). The calibrator of each drug item tests the parent compound or the respective metabolite. Once the antibodies of the binding sites are saturated, no labelled antibodies are retained in the capture zones, causing disappearance of the corresponding marking. While disappearance of a marking implies a positive result, incomplete disappearance of the marking, or a "faint line" should be interpreted as a negative result. This is exactly the opposite to commercially available urine pregnancy tests where presence of marking represents a positive result. The test is easy to read with the naked eye. The shortcoming nonetheless is the qualitative nature of these tests that represent only exposure in a highly variable time window (2-30 days or more depending on the analyte and use pattern).[6] Some commonly encountered drugs of abuse or malicious use such as gamma hydroxybuterate (GHB) and ketamine are not detected by a routine multi-drug screening panel. Immunoassay is also subject to cross-reactivity with other substances. For example, the kit may be falsely positive for tricyclic antidepressant in a patient prescribed diphenhydramine, quetiapine, carbamazepine, chlorpromazine, or cetirizine. A benzodiazepine panel typically screens for the metabolite oxazepam, but can be falsely negative for lorazepam and alprazolam because they are not metabolised to oxazepam.[4] Such non-specific screening may confuse the interpreting clinician about the true culprit agent. A hypothetical case can be used for illustration: a known opioid abuser presents with psychomotor agitation, fever, hypertension,

tachycardia, mydriasis and diaphoresis. Bedside urine multi-drug panel testing shows positive results for methamphetamine, morphine, and methadone. The most probable causative agent for the acute sympathomimetic toxidrome is methamphetamine, a central nervous system stimulant; positive results for morphine and methadone indicate exposure only. Based on the clinical picture and supplemented by knowledge of the bedside urine immunoassay results, the attending physician should treat the patient with cooling techniques, rehydration, and titrated doses of a sedative such as a benzodiazepine. Some centres have challenged the clinical applicability of routine qualitative urine toxicology screening while some reserve their use for specialist staff.[7,8]

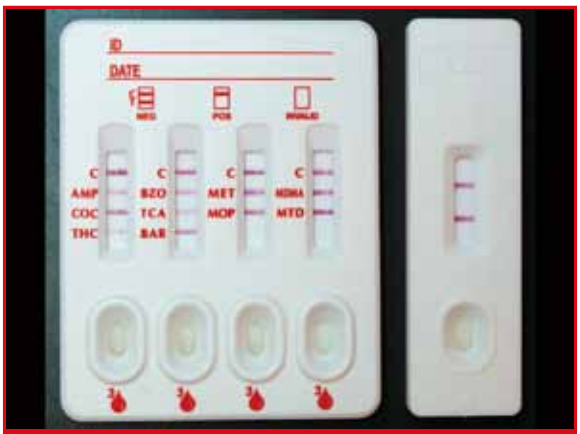


Figure 1: Bedside urine immunoassay kits for screening of abusive substances, from urine specimens produced by the author who had no previous exposure. Both kits showed negative results. Faint lines imply negative results. Left panel, ABON™ One Step Multi-line Screen Test Device. Right panel, ABON™ One Step Drug Screen Test Device for Ketamine.

New psychoactive substances (NPS) constitute an emergent challenge to physicians, toxicologists, and drug controlling authorities worldwide. They are structural or functional analogues of controlled substances, designed to mimic their desired pharmacological effects. Structurally speaking they are classified as cannabinoids (*e.g. cannabicyclohexanol, 5F-AKB48, JWH-018, JWH-073, HU-210*), substituted phenylethylamines (e.g. alkylated or fluorinated amphetamines, cathinones, mephedrone, methylone, *α-PVP, MDPV, 21I-NEOMe*), or synthetic opioids (*e.g. MT-45, AH-7921*). They may be marketed as plant food, bath salts, or research chemicals with cautionary statements such as "not for human consumption" to circumvent law enforcement and regulatory control. These "designer drugs" are not detectable by a bedside urine immunoassay kit or routine laboratory toxicology screening. They require a laboratory with expertise, sophisticated instruments such as high performance liquid chromatography-mass spectrometry (HPLC-MS) and a comprehensive drug library for detection. In Hong Kong, such standards can only be achieved by the Toxicology Reference Laboratory of the Princess Margaret Hospital and the toxicology laboratories of certain tertiary hospitals.[9] Consultation with a chemical pathologist is necessary to ensure optimum utilisation of these high-end services.

Commercial hair and nail analysis: not recommended

Hair and nail analyses may be offered by some commercial laboratories. They may be marketed as a reference to one's general nutritional and health status, and enable doctors to determine if mineral imbalances or heavy metals in the body are a potential cause of a patient's symptoms. This is not evidence based. While hair analysis may be applicable in a specific population group to determine exposure to a very specific toxin in a forensic or occupational settings, in general it provides only limited information about environmental exposure and does not address the questions about potential health effects. One of the few known potential applications is to determine whether women of reproductive age have been recently exposed to methyl mercury (at a level that would give rise to concern) by consuming contaminated fish. Nonetheless the presence of methylmercury in maternal hair does not provide substantial evidence to support causation of foetal developmental effects on an individual level. Even if the substances of interest are demonstrated in hair, linkage to endogenous or exogenous exposure cannot be established. An expert panel convened by the Agency for Toxic Substances and Disease Registry (ATSDR) in the United States determined that for most substances, insufficient data existed to allow prediction of health effects based on their concentration in hair.[10]

There is no international consensus regarding standard procedures for collecting, washing, and analysing hair samples. Hair grows at a very slow rate (0.35 mm daily for a normal scalp)[11] and analysis is subject to influence by shampoos and dyes, disproportional distribution of substances of interest in hair and various body compartments. For example, a seemingly high-normal content of zinc may preclude the diagnosis of zinc deficiency, but zinc content can be low at the tissue level and adversely affect protein and nucleic acid metabolism.[12] Determination of a reference range for elements in hair and nails requires internal and external validation of data by accredited laboratories, and adaptation of standards and regulations by government agencies and professional bodies.[13] Currently no standardised "normal range" of substances and trace elements exists for hair and nail samples. Values outside an individual laboratory reference range do not imply toxicity and need for treatment. There has been no population based study of the reference range for heavy metals and trace elements in hair and nails. A local case series of three children with hair samples sent to overseas centres for analysis revealed "abnormal" results for multiple elements. Unnecessary chelation therapies were nonetheless subsequently stopped following additional standard diagnostic tests.[14] Using a questionable test in patients with non-specific symptoms may produce false positive results and is vulnerable to medical fraud, as toxicology test services are potentially lucrative.[15] Policies and position statements by the American Medical Association and the Hong Kong College of Paediatricians have opposed the use of hair analysis to detect heavy metal exposure.[16,17]

Hair or nail testing for heavy metal screening should be discouraged in patients with nonspecific symptoms.

Again, proper clinical assessment for potential exposure to metals must include the precise exposure history including possible sources, route and dose of exposure, and symptoms present. A targeted physical examination to identify relevant physical signs should be performed before ordering tests based on clinical suspicion. Non-specific hair and nail tests for multiple metals may subject patients to potentially harmful diagnostic mislabelling and subsequent detrimental therapy.[5]

Laboratory report with extensive list of "recommendations": beware

Clinicians should be particularly careful if the laboratory report is supplemented by a long list of recommendations of supplements, vitamins, minerals, enzymes, or animal organ extracts; a long list of alleged "possible medical conditions" if any one of the substances lies outside the "reference range". It contradicts the foundation of medical practice in which relevant laboratory tests for a suspected condition should only follow proper history taking, and physical examination with some simple bedside investigations. The practice of prescribing therapy without a proper assessment and diagnosis should be discouraged.

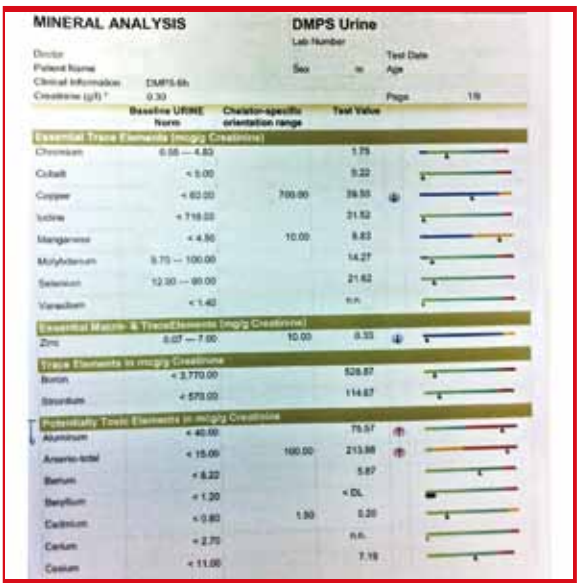
Say no to test reports from "provoked" urine specimen

Heavy metal is a common concern among parents who are distressed by their children's behavioural issues. Some may seek a clinician's opinion about an "abnormal" result from a commercial laboratory. Patients may have been given a chelating agent, such as DMPS (*2,3-dimercapto-1-propanesulfonic acid*), DMSA (*meso-2,3-dimercaptosuccinic acid*), or EDTA (*ethylenediaminetetraacetic acid*), before a specimen was saved. Chelation is an artificially enhanced affinity of chelating ligands for a metal ion, and can sequester metals from the body, usually in urine. Urine samples collected after chelation are said to be "provoked". Clinicians are advised to interpret such manipulated results with great caution.

There are standardised, clinically-proven and well validated methods to measure the presence of heavy metals in the body. Using mercury as an example, the patient should be advised to terminate potential sources of exposure, such as seafood, cosmetics and herbs, 1 to 2 weeks before measurement to reflect the exposure more accurately. A 24-hour urine sample, not a spot or a 4-hour or 6-hour sample saved within a truncated time frame, should be saved to avoid the influence of hydration status and food intake. Nonetheless "provoking" means mobilising the metals from other body compartments to urine using chelating agents, and the rate of mobilisation is greatest in the first few hours. This will cause a falsely elevated concentration, with risks of inappropriate diagnosis and erroneous administration of chelation therapy. Although a urine specimen is appropriate to screen for exposure to inorganic or elemental mercury that has a short half-life in blood, a whole blood mercury level is the preferred measurement for organic mercury that is excreted primarily in faeces.[18]

To date, there are no externally validated reference ranges for heavy metal concentrations in urine with a "provoked" urine sample. Chelation therapy based on these results is not evidence-based and potentially harmful. Numerous unfounded claims for the health benefits of chelation therapy have been made by various bodies, such as a reduction in cardiovascular risks,[19] improved quality of life in patients after heart attack,[20] improvement in peripheral vascular disease,[21] treatment for autism,[22] and cancer.[23] None of these claims has been substantiated by well-designed clinical trials.

Inappropriate use of chelating agents involves risks. Side effects may arise even from appropriate chelation therapy, and include dehydration, hypocalcaemia, renal impairment, deranged liver function, hypotension, allergic reactions and essential mineral deficiencies. Inappropriate chelation, by itself a costly burden, imposes the risk of harm, neurodevelopmental toxicity, teratogenicity and death.[5] A case of Stevens-Johnson syndrome in a child with chronic mercury exposure and DMPS therapy has been reported.[24]


MINERAL ANALYSIS

DMPS Urine

Figure 2: Report from an overseas commercial laboratory using urine specimen saved 6 hours after administration of a chelating agent DMPS. Patient did not have any compatible symptoms and signs. The spurious results from questionable tests were not interpretable at all.

For any doubts, consult an expert

The Hong Kong Poison Control Network was established in 2007, with joint collaborative efforts by the Hospital Authority (HA), the Department of Health and the Chinese University of Hong Kong. The Hong Kong Poison Information Centre located at the United Christian Hospital provides a 24-hour telephone consultation service to local healthcare professionals. As part of the poisoning surveillance, it receives reports of all poisoning cases from public emergency departments. Clinical toxicology clinics are established at the Prince of Wales Hospital, United Christian Hospital, and Queen Mary Hospital, and are open to referrals from local medical practitioners.

Conclusion

Increased health awareness of patients as well as diagnostic vigilance among health professionals are expected to contribute to an increased demand for toxicology tests in the foreseeable future. Clinical judgement remains the most reliable weapon in successful poisoning management. Physicians should be familiar with the implications and limitations of tests to be arranged. To have a meaningful result, the ordered tests should be based on clinical suspicion and processed using standardised methods in accredited laboratories. Tests on a "provoked" urine sample or a sample collected during a truncated collection period are unreliable. Consultation with an expert should be considered when there is any doubt about the care of a patient with confirmed or suspected poisoning.

References

1. Development Bureau of the Government of the Hong Kong Special Administrative Region. Report of the task force on investigation of excessive lead content in drinking water [Internet]. October 2015. Available from: http://www.devb.gov.hk/filemanager/en/Content_3/TF_Final_Report.pdf [Accessed 4th January 2016]
2. Leikin JB. Foreword. Disease-a-Month [Internet]. 2014;60(11):508. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0011502914001424
3. Hoffman RS et al. Initial evaluation of patient: vital signs and toxic syndromes. Goldfrank's Toxicologic Emergencies 10th edition. 2015 Chapter 3; 26-29
4. Hoffman RJ, Nelson L. Rational use of toxicology testing in children. Curr Opin Pediatr [Internet]. 2001 Apr;13(2):183–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11317063
5. The American College of Medical Toxicology and The American Academy of Clinical Toxicology. Choosing Wisely® Campaign: Ten Things Physicians and Patients Should Question [Internet]. 26th March 2015. Available from: http://www.choosingwisely.org/societies/american-college-of-medical-toxicology-and-the-american-academy-of-clinical-toxicology/ [Accessed 4th January 2016]
6. Wu AHB, McKay C, Broussard L a., Hoffman RS, Kwong TC, Moyer TP, et al. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: Recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem. 2003;49(3):357–79.
7. Albertadoctors.org. Choosing Wisely Resources: Alberta Medical Association [Internet]. 2016. Available from: https://www.albertadoctors.org/leaders-partners/choosing-wisely-alberta/choosing-wisely-resources [Accessed 4th January 2016]
8. Watson I. Laboratory analyses for poisoned patients: joint position paper. Ann Clin Biochem 2002;39:328–39.
9. Tang MHY, Ching CK, Tse ML, Ng C, Lee C, Chong YK, et al. Surveillance of emerging drugs of abuse in Hong Kong: validation of an analytical tool. Hong Kong Med J [Internet]. 2015 Apr;21(2):114–23. Available from: http://www.hkmj.org/earlyrelease/hkmj144398.htm
10. Harkins DK, Susten AS. Hair analysis: exploring the state of the science. Environ Health Perspect [Internet]. 2003 Apr;111(4):576–8. Available from: http://www.ehponline.org/ambra-doi-resolver/10.1289/ehp.5842
11. Bergfeld WF, Mulinari-Brenner F. Shedding: how to manage a common cause of hair loss. Cleve Clin J Med [Internet]. 2001 Mar;68(3):256–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11263854
12. Hambidge KM, Krebs NF. Zinc deficiency: a special challenge. J Nutr. 2007 Apr;137(4):1101-5.
13. Druyan ME, Bass D, Puchyr R, Urek K, Quig D, Harmon E, et al. Determination of reference ranges for elements in human scalp hair. Biol Trace Elem Res [Internet]. 1998 Jun [cited 2015 Dec 15];62(3):183–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9676882
14. Poon WT, Ling SC, Chan AYW, Mak TWL. Use of hair analysis in the diagnosis of heavy metal poisoning: report of three cases. Hong Kong Med J [Internet]. 2004 Jun;10(3):197–200. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15181225
15. Seidel S, Kreutzer R, Smith D, McNeel S, Gilliss D. Assessment of commercial laboratories performing hair mineral analysis. JAMA [Internet]. 2001 Jan 3;285(1):67–72. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.285.1.67
16. American Medical Association (AMA). Hair analysis: a potential for abuse. Policy No. H-175.995. Chicago: AMA; 1994.
17. Ip P, Ko P, Lam C, Nelson T, Wong V. Hong Kong College of Paediatricians Position Paper on Exposure to Lead and Mercury in Children and Chelation Therapy Exposure to Lead and Chelation Therapy. 2010;(March):103–8.
18. Fan KL, Chan CK, Lau FL. Mercury exposure: the experience of the Hong Kong Poison Information Centre. Hong Kong Med J [Internet]. 2011;17(4):292–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21813897
19. Ernst E. Chelation therapy for coronary heart disease: An overview of all clinical investigations. Am Heart J. 2000 Jul;140(1):139-41.
20. Lamas GA, Goertz C, Boineau R, Mark DB, Rozema T, Nahin RL, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. Jama [Internet]. 2013;309(12):1241–50. Available from: http://jama.jamanetwork.com/article.aspx?articleid=1672238
21. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. Circulation [Internet]. 1997 Aug 5;96(3):1031–3. Available from: http://circ.ahajournals.org/content/96/3/1031.long
22. Davis TN, O'Reilly M, Kang S, Lang R, Rispoli M, Sigafoos J, et al. Chelation treatment for autism spectrum disorders: A systematic review. Res Autism Spectr Disord [Internet]. 2013 Jan;7(1):49–55. Available from: http://www.sciencedirect.com/science/article/pii/S1750946712000724
23. Buss JL, Torti FM, Torti S V. The role of iron chelation in cancer therapy. Curr Med Chem [Internet]. 2003 Jun;10(12):1021–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12678674
24. Van der Linde AA, Pillen S, Gerrits GP, Bouwes Bavinck JN. Stevens-Johnson syndrome in a child with chronic mercury exposure and 2,3-dimercaptopropane-1-sulfonate (DMPS) therapy. Clin Toxicol (Phila) [Internet]. 2008;46(5):479–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18568806

mehk Meetings & Exhibitions Hong Kong

HONG KONG

THE WORLD'S MEETING PLACE

香港 HONG KONG
ASIA'S WORLD CITY

As Asia's premier destination for meetings, incentive travel, conventions and exhibitions, Hong Kong is where you can turn boundless potential into reality. Providing sophisticated infrastructure, professional services and more, this gateway to China ensures success for the most important events in the world.

mehongkong.com

LEARN MORE NOW

Balancing Risk and Benefit in Drug Therapy

Prof Cyrus R Kumana

BSc, MB, FRCP (Can, Lond, Edin, Glasg), FHKCP, FHKAM

Department of Medicine, The University of Hong Kong

Prof Cyrus R Kumana

Balancing risks against benefits is a universal conundrum for all living creatures. It applies to all aspects of life and has wide ranging connotations that extend to virtually all manner of interventions affecting many facets of life, whether relevant to individuals and/or communities. For example, one may opt for the greater good of the greatest number rather than the greater good of any one individual. Similarly, behavioural reactions such as fighting or waging war to achieve perceived desirable gains at the risk of possible harm also involve balancing acts, as do the social habits and political policies we opt to follow or enact. Balancing the benefits and risks of therapeutic interventions is a very special kind of dilemma that is increasingly based on the results of published clinical trials that may not be truly representative of routine clinical practice in the hospital or the community. In the absence of any other alternatives, and provided such studies are peer-reviewed, they nevertheless provide at least a modicum of evidence to support decisions. Against this background, this article concentrates on a very narrow area, namely, balancing the risks and benefits conferred by drug therapy in humans.

In man, all such considerations ultimately entail judgmental decisions and to a variable extent they are based on subjective perceptions as well as objective data. Prevailing patient circumstances (geography, ethnicity/genetics, affordability, convenience, quality of life issues) inevitably have an influence. This means that the judgements made can differ between places and between persons, depending on the population or individual to be targeted. Notwithstanding this caveat, the following pages address several of the most important pertinent principles about this topic, by reference to iconic studies in which these issues were critical.

Evaluation of Outcomes: In any exercise to balance benefits and risks of drug therapy it is imperative to concentrate on outcomes. In this context, it is particularly important to recognize *the fallacy of relying on proposed surrogate markers as opposed to hard outcomes*, especially as resorting to surrogates often enables statistically significant 'benefits' to be inferred with very small patient numbers, thereby obscuring important effects on hard outcomes. For example, in the two trials known by the acronym CAST (Cardiac Arrhythmia Suppression Trials I & II)[1-2] and many others, antiarrhythmic drug treatment was superior to placebo in the suppression of asymptomatic ventricular arrhythmias. Yet fortuitously, due to recruitment of sufficient patient numbers, paradoxically increased arrhythmic mortality became apparent. *Assessing benefits exclusively in terms of the primary endpoint* is another important shortcoming, as failure to consider all other important *outcomes of interest* could result in undesirable consequences. This principle is exemplified in one of the first large-scale, placebo-controlled, randomized, double-blind scale trials of lipid lowering therapy that involved 10,627 healthy male adults with a high cholesterol level.[3] After treatment for an average of 5.3 years, there was a statistically significant 17% reduction in fatal and no-fatal myocardial infarction (the primary outcome) among those prescribed regular oral clofibrate. Nonetheless active treatment was also associated with a statistically significant 19% increase in all-cause mortality. Thus, whilst clofibrate recipients enjoyed a favourable impact on the outcome of interest, they also endured an excess of deaths due to unrelated causes (whatever the reason). *The importance of intention to treat outcome analyses* became an established strategy after publication of the study with the acronym ART (Anturan Reinfarction Trial).[4] The trial was heavily criticised for its reliance only on a per-protocol analysis of outcomes. This double-blind, randomized trial that involved 1558 post-myocardial infarct patients was terminated early, as it was inferred that the benefits of therapy with Anturan (suphinpyrazone, a uricosuric with anti¬platelet activity) were so compelling that to withhold giving it to the controls would be unethical. Basically, the ART investigators carried out a so-called efficacy analysis after a mean patient follow-up of 16 months, whereby outcomes were only counted if they ensued 7 days after starting treatment (the time taken for Anturan's antiplatelet activity to become established) and patient compliance with therapy was acceptable. Based on this analysis, actively treated patients fared very much better than the controls. However, it transpired that there was an excess of early deaths (within the first 7days) among Anturan recipients. An efficacy analysis can only assess benefits or harm in those who take the treatment as intended, whilst an-intention-to-treat (or effectiveness) analysis assesses outcomes in those to whom the treatment is offered, which is after all what really matters.

Absolute versus Relative Benefits of a Drug: An important aspect when balancing the benefits and risks of drug therapy is the distinction between relative and absolute values. Only the latter can enable clinicians to make genuinely informed decisions. Physicians generally understand parameters such as RRR (Relative Risk Reduction) and its converse RR (Relative Risk), sometimes expressed as percentages. Nonetheless doctors are not necessarily mathematically adept and so

often find it difficult to come to terms with figures such as 0.086, which is the ARR (Absolute Risk Reduction) for myocardial infarction or coronary heart disease death derived from the 4S study[5] of high risk patients treated with simvastatin for an average of 5.4 years. In contrast, it is easier to comprehend a NNT (*Number Needed to Treat*) of 12 (i.e. one patient avoiding such an event for every 12 who are treated), that is another way of expressing the absolute risk reduction over the same period.† Moreover, this parameter can be made even more meaningful by adjustment for treatment duration; the NNT/year value in the 4S trial was 64.[6] In the AFFIRM trial[7] of rhythm versus rate control for atrial fibrillation, derivation of NNTs (or more correctly '*number needed to harm*' (or NNH)) for rhythm control can be particularly revealing for comparing risks.[8] In the latter trial, in rhythm control patients the calculated RRs for hospitalization and for Torsade (a drug adverse effect) based on the raw data was 112 and 598% respectively, which might suggest that Torsade was a much more prevalent complication. On the contrary, the respective NNH/year values were 47 and 712,* indicating that for every 47 patients assigned to rhythm control 1 more was liable to be hospitalized per year, whilst for Torsade (a complication that is much less common) the corresponding figure was 712.

Balancing Benefits versus Harm to Society: One such area is consideration of value for money in terms of drug expenditure, especially for medicines that are very costly and achieve very limited gains (alluded to in Professor BMY Cheung's article). This facet of risk/benefit balancing is quite commonly undertaken in public hospitals, where it may be easier to implement/mandate such policies than elsewhere. An example is the automatic substitution of generic (or even bio-similar) drugs that have been reliably validated for comparable safety and efficacy, so as to accrue cost savings that can be expended for other purposes.[9,10] Yet another facet of benefitting society without jeopardising the safety of individual patients involves so-called *Antibiotic Stewardship Programmes* that have been set-up internationally as well as locally.[12,13] Such programmes aim to curtail their profligate use and reduce undue influence by pharmaceutical manufacturers, in an attempt to curb the development and spread of antibiotic resistance for the greater good of society. Like automatic substitution, these strategies usually evolve in hospitals or academic institutions, but it is possible that all such initiatives can have a trickledown effect on prescribing behavior at a community level. Whilst these aspects of balancing the individual benefits and societal risks of drug therapy may not seem of direct relevance to many practitioners and their patients in the community, they have nevertheless become major issues that are constantly discussed in medical journals. Hopefully, ways and means can be found to implement them more widely and effectively so as to impact doctors who practice outside as well as inside hospitals.

Conclusion: Balancing the benefits and risks of drug therapy is a judgmental decision that must take stock of each patient's circumstances in the light of available evidence. Notably, i) deciding whether the benefits of a treatment can outweigh the risks depends on efficacy analyses, ii) whether such benefits do outweigh risks in those to whom it is offered depends on intention to treat (effectiveness) analyses, and iii) deciding whether such treatment is worthwhile depends on NNT (and NNH) values.[14] Finally, the efficiency of arriving at appropriate drug therapy decisions may also be facilitated and/or enhanced by drug therapy stewardship programmes and automatic drug substitution policies.

References

1. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med. 1989;321:406-12.
2. The Cardiac Arrhythmia Suppression Trial-II Investigators. Effect of antiarrhythmic agent moricizine on survival after myocardial infarction: the Cardiac Arrhythmia Suppression Trial-II. N Engl J Med 1992;327:227-33.
3. Oliver MF, Heady JA, Morris JN, et al. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 1978;40:1069-118.
4. The Anturan Reinfarction Trial Research Group. Sulfinpyrazone in the prevention of sudden death after myocardial infarction. N Engl J Med 1980;302:250-6.
5. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol of cholesterol lowering in 4444 patients with coronary heart disease. Lancet 1994;344:1383-9.
6. Kumana CR, Cheung BMY, Lauder IJ. Guaging the impact of statins using number needed to treat (Contempo article). JAMA 1999;282;1899–901.
7. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825–33.
8. Kumana CR, Cheung BMY, Cheung GTY, Ovedal T, Pederson B, Lauder IJ 2005. Brit J Clin Pharmac 60:347-54. Rhythm versus rate control of atrial fibrillation meta-analysed by number needed to treat.
9. Duerden MG and Hughes DA. Generic and therapeutic substitutions in the UK: are they a good thing? Br J Clin Pharmacol 2010;70(3): 335–41.
10. Miletich J, Eich G, Grampp G, et al. Biosimilars 2.0: guiding principles for a global "patients first" standard. MAbs 2011;3(3):318-25.
11. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke Study Group. N Engl J Med 1995;333:1581-7.
12. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Clin Infect Dis 2007;44:159–77.
13. Cheung VC, To KK, Li IW, et al. Antimicrobial stewardship program directed at broad spectrum intravenous antibiotic prescription in a tertiary hospital. Eur J Clin Microbiol Infect Dis 2009;28:1447-56.
14. Haines B. Can it work? Does it work? Is it worth it? The testing of health care interventions is evolving. (Commentary) BMJ. 1999;319 (7211):652-3.

† NNTs can also be used to describe absolute risk reductions or absolute risks following one-off interventions, e.g. In the NINDS trial[11] of thrombolysis for acute ischaemic stroke, the calculated NNH for sustaining a fatal or symptomatic intracranial bleed within 36 hours turns out to be 17.

* The RR and NNH/year values for Torsade are not shown in reference 8 but can be readily calculated.

Experience

Samsca® (tolvaptan)

15 mg tablet

Experience the first and only oral vasopressin V_2-receptor antagonist that increases

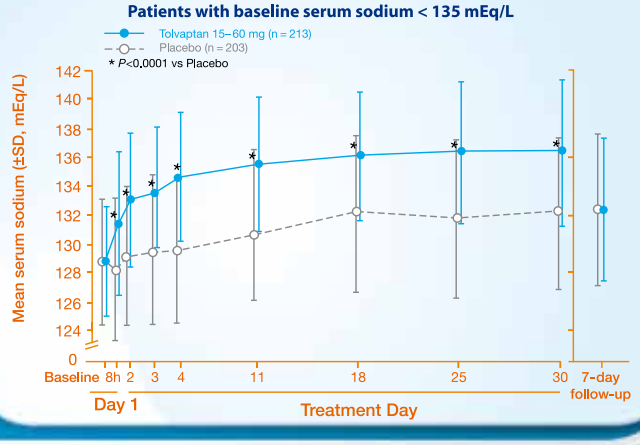
FREE V_2 WATER CLEARANCE

and serum sodium concentrations.

Samsca® promotes electrolyte-free water clearance[1]

- Direct antagonism of the V2-receptors increases urine water excretion, resulting in:
  - An increase in free water clearance (aquaresis)
  - A decrease in urine osmolarity
  - An increase in serum sodium concentration

Pooled SALT (Study of Ascending Levels of Tolvaptan in hyponatremia): analysis of mean serum sodium (±SD, mEq/L) by visit



Indication[2]

SAMSCA® is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Abbreviated Prescribing Information

Presentation: Tablets 15mg or 30mg of tolvaptan. **Indication:** SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). **Dosage:** To be initiated in hospital due to need for evaluation of therapeutic response. The usual starting dose for SAMSCA is 15mg administered once daily without regard to meals. Increase the dose to 30mg once daily, after at least 24 hours, to a maximum of 60 mg once daily, as needed to achieve the desired level of serum sodium. Limit treatment duration to 30 days. **Contraindications:** Hypersensitivity to any component of Samsca. Urgent need to raise serum sodium acutely. Anuria. Hypovolaemic hyponatremia (worsening). Hypernatremia. Patients who cannot perceive or appropriately respond to thirst. Concomitant use of strong CYP3A inhibitors. Pregnancy. Breastfeeding. **Warnings and precautions:** Tolvaptan should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Tolvaptan has not been in a setting of urgent need to raise serum sodium acutely. For such patients, alternate treatment should be considered. Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (eg., >12mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. Caution should be exercised to ensure patients have adequate access to water and not become overly dehydrated. Urinary outflow must be secured to avoid risk of developing acute urinary intention. If hepatic injury is suspected, discontinue SAMSCA. Avoid use in patients with underlying liver disease. Concomitant use of SAMSCA with other treatments for hyponatremia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium and is therefore not recommended. **Drug interactions:** Caution with: co-administration with CYP3A inhibitors, inducers and substrates. P-gp inhibitors, and digoxin. Concomitant use with hypertonic saline is not recommended. The effect of vasopressin analogues such as desmopressin may be attenuated in patients using such analogues to prevent or control bleeding when co-administered with SAMSCA. **Adverse reactions:** The following adverse reactions were reported (>2%) in clinical trials in hyponatremia: Dry mouth, constipation, thirst, asthenia, pyrexia, hyperglycemia, anorexia, pollakiuria or polyuria. See full package insert for further details and other undesirable effect. **Overdosage:** If overdose occurs, estimation of the severity of poisoning is an important first step. Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated. Please refer to full package insert for further details.

Reference: 1. Schrier RW, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006;355:2099–2112. 2. Samsca package insert

SMC 201601 (approved in JAN 2016)

Further information available upon request.

Otsuka Otsuka Pharmaceutical (H.K.) Ltd.
10/F, Phase 1, China Taiping Tower, 8 Sunning Road, Causeway Bay, Hong Kong.
Tel: 2881 6299 Fax: 2577 5206

Are We Ready to Use Biosimilars in the Treatment of Rheumatic Diseases?

Dr Tommy Tsang CHEUNG

MBBS(HK), MRCP (UK), FHKCP, FHKAM (Medicine)
Clinical Assistant Professor
Division of Clinical Pharmacology and Therapeutics
Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong

Dr Tommy Tsang CHEUNG

Introduction

The introduction of biologics has revolutionized the treatment of rheumatic diseases, especially for patients with inflammatory arthritis. Biologics not only improve the clinical outcomes, they also enhance quality of life. Nonetheless the overall number of prescriptions for biologics remains limited when compared with that for chemical drugs because biologics are far too expensive. In 2012, the total annual sales of the top 3 TNF-α inhibitors for rheumatic diseases reached US$ 30 billion per year. This is equivalent to a financial burden of US$ 10,000 to 30,000 per patient per year[1].

Since many patients are deprived access to biologics due to financial constraints, many developing countries have manufactured 'bio-copies' (Table 1). These products cannot be considered biosimilars because comparative analytical or clinical studies with the reference biological products are lacking. Nonetheless following the expiry of the patent for the first TNF-α inhibitor, infliximab, many manufacturers have sought to develop 'official' follow-on biological products, known as biosimilars. Both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have published regulatory guidelines on biosimilars to ensure comparability with the reference biological products, in terms of protein structure, pharmacological properties, clinical efficacy and safety[2,3]. The introduction of biosimilars in clinical use may substantially reduce the burden on the public health system, and improve access to these effective but yet expensive agents.

Table 1. Biocopies currently in use for the treatment of rheumatic diseases (Not subjected to EMA/ FDA standards for comparability at the time of approval)

Reference biologics	Bio-copies	Manufacturers	Marketed countries
Etanercept	Yisaipu	Shanghai CP Goujian Pharmaceutical Co.	China
Etanercept	Etanar	Shanghai CP Goujian Pharmaceutical Co.	Colombia
Etanercept	Infinitam	Probiomed	Mexico
Rituximab (Withdrawn)	Kikuzubam	Probiomed	Bolivia, Chile, Mexico, Peru
Rituximab	Reditux	Dr. Reddy's Laboratories	Ecuador, Bolivia, Chile, Paraguay, Peru, India

Before we prescribe biosimilars to our patients, there are a few issues that we need to address[4]. This article will discuss the manufacturing process for biosimilars, the regulatory requirements for their approval, issues of indication extrapolation and interchangebility between the reference biological products and biosimilars.

Are biosimilars structurally identical to the reference biological products?

Unlike a chemical drug, which is typically manufactured through chemical synthesis, the production of a biological product relies on a sophisticated manufacturing process. It is usually manufactured in a living system such as a microorganism, plant or animal cell. The recent advancement in biotechnology has enabled many biological products to be produced by recombinant DNA technology. They are a large and complex protein with well-characterized conformational structure, determined by the primary amino acid sequences and post-translation modifications.

A subtle change in the manufacturing process, such as using different growth media or operating condition, can significantly alter the post-translational modifications of the protein molecule (Figure 1). Post-translational modifications e.g. glycosylation, methylation, oxidation and deamidation, are key factors that determine the tertiary and quaternary structure of the biological product[5], that in turn may affect its affinity, functional activity and immunogenicity.

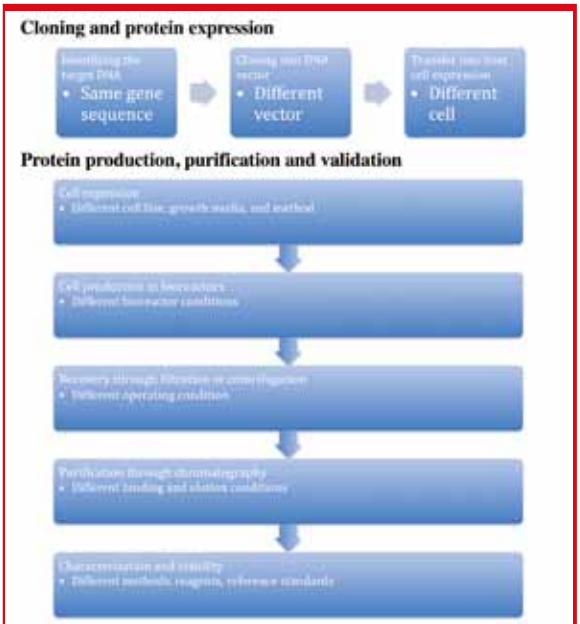


Figure 1. Potential alternations in the m manufacturing process of biological products

If the manufacturing processes of the reference biological product require modification, the manufacturer must carry out extensive analysis to demonstrate the comparability of the biological product. Even though the manufacturing process is highly regulated, micro-heterogeneity is still common in different batch productions[6].

Once the patent of the reference biological product has expired, biosimilar manufacturers can gain knowledge of its amino acid sequence, although they will not be given the proprietary manufacturing data. Manufacturers of a biosimilar will likely follow a different manufacturing process. Therefore, development of a biosimilar with an identical conformational structure to the reference biological product is virtually impossible[7].

Although recent advances in analytical techniques enable biological products to be extensively characterized with respect to their physiochemical and biological properties, such as higher order structures and functional characteristics, current analytical methodologies may not be able to detect all relevant structural and functional differences between a biosimilar and its reference biological product[8]. In addition, there may be incomplete understanding of the relationship between the structural attributes and its clinical performance. Clinical trials are mandatory to demonstrate that no clinically meaningful difference exists between the biosimilar and its reference biological product[9].

What are the requirements for approval of biosimilars?

Europe was the first region to establish a specific regulatory approval process for biosimilars.

The "concept of similar biological medicinal product" was adopted by the European Union legislation in 2004 and came into effect in 2005[10]. The EMA developed guidelines on biosimilars and published product specific guidelines on monoclonal antibodies in 20123. Following the EMA, the World Health Organization (WHO) published guidelines to present globally acceptable principles for biosimilar approval[11]. These guidelines represented an important step in ensuring consistency in the evaluation and regulation of biosimilars. Several countries have already adopted the principles to supplement their own guidelines for biosimilar approval. The United States has lagged behind Europe in this field, as detailed guidelines on the assessment of biosimilarity were only published in 2012 by the FDA2.

According to these guidelines, it is mandatory for the manufacturers of biosimilars to demonstrate adequate comparability with the reference biological products in terms of the pharmacological characteristics[12, 13] (Table 2).

In addition to the analytical characterization of biosimilars, comparability should also be confirmed by adequately powered, double blind, randomized controlled trials, as it is the only way to evaluate any clinically meaningful difference between a biosimilar and its reference biological product. It is important to define the main outcome measures and dosage used for a particular indication that is known to be sensitive enough to detect potential differences between the biosimilar and its reference biological product.

Once the endpoint has been selected for comparison, a decision on the appropriate trial design should be made i.e. equivalence or non-inferiority design. The choice of the design has implications for both the sample size needed, as well as the interpretation of data. The equivalence design is preferred by the EMA and FDA because it follows the concept of comparative assessment more closely. In essence, equivalent efficacy of two medicinal products means they have similar efficacy, and any observed difference is of no clinical relevance.

Selection of the primary efficacy endpoint and statistical design of the confirmatory clinical trial is a multi-step process that requires a clear understanding of the comparability margin. It should represent the largest difference in efficacy that would not matter in clinical practice. By its nature, the comparability margin for any given efficacy endpoint is a clinical judgment and often is not well established, so choice of margin size must be well justified, usually based on a combination of expert opinions and published analyses.

Table 2. FDA and EMA Requirements for the approval of biosimilars and the analytical assays that can be used

Structural Characteristics	FDA &EMA Requirements	Analytical assays that can be used
Amino acid sequence	Must be identical	RP-HPLC LC-ESI-MS LC-ESI-MS peptic mapping
Higher order structure	Must be as similar as possible to the reference biological product, which do not impact upon clinical efficacy, safety and immunogenicity	LC-ESI-MS peptide mapping Elman assay FTIR Antibody conformational array X-ray crystallography DSC
Post-translational modifications		LC-MS peptide mapping CE-SDS HPLC HPAEC-PAD
Potency	Must match with the reference biological product	ELISA SPR Cell based neutralization assay Cell based apoptosis assay Cell based CDC assay

CD: circular dichroism spectroscopy, CE-SDS: capillary electrophoresis (sodium dodecyl sulfate), DSC: differential scanning calorimetry, ELISA: enzyme linked immunosorbent assay, FTIR: Fourier transform infrared spectroscopy, HPAEC-PAD: anion exchange chromatography with pulse amperometric detection, LC-ESI-MS: liquid chromatography electrospray ionization mass spectrometry, RP-HPLC: reversed phase high performance liquid chromatography, SPR: surface plasmon resonance

Is extrapolation of clinical data from one indication to another possible for biosimilars?

Extrapolation of clinical data allows the approval of a biosimilar for a therapeutic indication for which it

has not been clinically evaluated. Both EMA and FDA permit extrapolation across indications for biosimilars because it is reasonable to assume that the biosimilar will behave similarly to its reference biological product in different indications. Nonetheless extrapolation may be less appropriate if the mechanism of action is different between indications. In view of this, EMA and FDA have outlined measures to address the concerns regarding indication extrapolation (Table 3).

Table 3. EMA and FDA response to concern regarding extrapolation of clinical data

Concern	EMA	FDA
Mechanism of action may be distinct in each therapeutic indication	Extrapolation will be considered on a case-by-case basis. Where the MOA differs between indications or are not fully understood, separate clinical trials are likely to be necessary	
For a given mechanism of action, several mechanisms may exis	Almost superimposable biological data must be provided, covering all functional aspects of the agent, even if not considered clinically relevant. Where MOA is not fully understood, separate clinical trials are likely to be necessary	
Risk of undertreating patients or varied safety profiles in different patient groups	Data should be produced using a patient population and clinical endpoint most sensitive to detect clinically meaningful differences in efficacy and safety	
Patient characteristics may influence response	Homogeneous population should be used	Careful consideration must be given to co-morbidities, concomitant medications and inter-subject variability

In rheumatoid arthritis, TNF-α inhibitors are thought to act predominantly through the neutralization of soluble and trans-membrane TNF-α. In other conditions such as Crohn's disease, signaling through membrane associated TNF-α and Fcγ receptor may play a more important role in apoptosis or antibody dependent cellular cytotoxicity[14]. This explains why Etanercept is not effective in inflammatory bowel diseases. Accordingly, the comparative data in rheumatoid arthritis may not support comparable efficacy in all indications. Subsequent indication extrapolation of biosimilars of TNF-α inhibitors from inflammatory arthritis to inflammatory bowel diseases was not granted in Canada.

Even when the mechanism of action is the same across different indications, the FDA recommended that data should be produced using a patient population and clinical endpoint most sensitive to detect clinically meaningful differences in efficacy and safety. The immunogenicity profile of biosimilars should also be characterized before extrapolation to other indications is sought. It should be tested in the patient population that carries the highest risk of an immune response and immune mediated adverse events[2].

Can we use the biosimilars and the reference product interchangeably?

Interchangeability must be supported by data showing that the biosimilar is likely to produce the same clinical results as its reference biological product. An interchangeable biosimilar must be able to substitute its reference biological product in any patient without introducing new risks or reducing efficacy. In addition, a biosimilar that fulfils the interchangeability standards may be substituted for its reference biological product by the pharmacy without authorization of the health-care provider.

The EMA does not have the authority to designate a biosimilar as interchangeable with its reference biological product, but the new US Biologics Price Competition and Innovation Act allows the FDA to formally designate a biosimilar interchangeable. Nevertheless biosimilars are currently not deemed interchangeable with their reference biological products. A good lesson was learned from cases of red cell aplasia in renal dialysis patients who were prescribed subcutaneous epoetin-α in 1990s. After an intensive investigation, the most likely cause was a formulation change that led to antibody formation against all circulating erythropoietin. Removal of human serum albumin from the epoetin-α formulation and its replacement with polysorbate 80 and glycine as stabilizers was suggested as the primary cause. This also illustrates the importance of post marketing pharmaco-vigilance of biosimilars. Using biosimilars and the reference biological products interchangeably may complicate an effective pharmaco-vigilance program, as it may subvert the ability to attribute immunogenicity or other safety related problems to the appropriate agent. A patient may then be obliged to stop both the biosimilar and reference biological product if there are complications.

Conclusion

As many of the patents of biologics are approaching their expiry date, biosimilars will be available in the market very soon. Although they offer a great potential for cost saving, it is important to understand the difference between a biosimilar and its reference biological product. To attain biosimilar status, it must be proven comparable with its reference biological product in terms of the protein structure, pharmacological properties, clinical efficacy and safety. EMA, WHO and FDA have already formulated guidelines for regulatory approval to ensure the quality of biosimilars.

Despite these stringent approval requirements, a biosimilar cannot be identical to its reference biological product. We must understand all the aspects that contribute to the differences between biosimilars and reference biological products, and use biosimilars vigilantly.

The American College of Rheumatology updated the position statement on biosimilars in February 2015[15]. Regarding the possibility of substitution, the committee suggested that the decision should only be made by the physician and compulsory switching to a biosimilar by a dispenser should not be allowed for economical reasons without advance consent from the physician. The committee suggested that biosimilars must have distinct names that allow them to be distinguished from each other and their reference biological products[2].

Based on the available data and regulatory guidelines,

many countries have developed their own position statements on the use of biosimilars, focusing on the choice of biosimilar versus reference biological product, interchangeability and post marketing pharmaco-vigilance (Table 4). Until local guidelines on the use of biosimilars are available, physicians can consider these to be a general guide before prescribing biosimilars to patients with rheumatic diseases.

Table 4. Position statement on the use of biosimilars in different countries

Countries	Drug selection	Interchangeability	Pharmaco-vigilance
United Kingdom[22]	A choice for patients initiating a new biologic therapy Not support a universal mandate that all patients should start a biosimilar purely to save costs.	Substitution only with the consent of the prescribing clinician	Registration with the BSR biologic registers Should undergo robust technology appraisals Use the brand names in all appraisal an guidance documentation
Italy[23]	Use of biosimilars in children needs to be carefully investigated	Automatic substitution not allowed Clinician's responsibility to decide on switching Use different names	Surveillance for safety and immunogenicity Use different names
Portugal[24]	Therapeutics choice must primarily be dictated by patient safety concerns The less expensive drug is a reasonable first therapeutic choice in naïve patients	Automatic substitution not acceptable Switching must be performed upon consent of the physician Prescription must be performed by brand name	Immunogenicity must be adequately assessed Robust pharmaco-vigilance must be assured
Spain[25]	the choice of an innovative drug or biosimilar is the responsibility of the prescribing physician	Substitution not permitted	Implement appropriate measured agreed by the Technical committee of the Spainish pharmco-vigilance system

References

1. Huggett B, Hodgson J, Lahteenmaki R. Public biotech 2009-the numbers. Nat Biotechnol 2010;28(8):793-9.
2. Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 2015.
3. European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies- non clinical and clinical issues. 2012.
4. Cheung BMY. What Physicians Need to Know About Biosimilars. Hong Kong J Radiol 2013;16(Suppl):S50-S54.
5. Kozlowski S, Woodcock J, Midthun K, et al. Developing the nation's biosimilars program. N Engl J Med 2011;365(5):385-8.
6. Schiestl M, Stangler T, Torella C, et al. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol 2011;29(4):310-2.
7. Pani L, Montilla S, Pimpinella G, et al. Biosimilars: the paradox of sharing the same pharmacological action without full chemical identity. Expert Opin Biol Ther 2013;13(10):1343-6.
8. Berkowitz SA, Engen JR, Mazzeo JR, et al. Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nat Rev Drug Discov 2012;11(7):527-40.
9. Azevedo VF. Biosimilars require scientifically reliable comparative clinical data. Rev Bras Reumatol 2013;53(1):129-31.
10. European Medicines Agency. Guideline on similar biological medicinal products. 2005.
11. World Health Organization. Expert committe on biological standardization. Guidelines on evaluation of similar biotherapeutic products. 2009.
12. Epstein MS, Ehrenpreis ED, Kulkarni PM, et al. Biosimilars: the need, the challenge, the future: the FDA perspective. Am J Gastroenterol 2014;109(12):1856-9.
13. Chugh PK, Roy V. Biosimilars: current scientific and regulatory considerations. Curr Clin Pharmacol 2014;9(1):53-63.
14. Tilg H, Moschen A, Kaser A. Mode of function of biological anti-TNF agents in the treatment of inflammatory bowel diseases. Expert Opin Biol Ther 2007;7(7):1051-9.
15. American College of Rheumatology. Position statement on biosimilars. 2015.

TIME SAVING
LIFE CHANGING

Enantone 1, 3 & 6 months DPS
for prostate cancer*: Introducing a unique delivery system[1,2,3,]

*Enantone 1 month DPS 3.75mg is indicated for Prostate cancer. Enantone 3 month DPS 11.25mg is indicated for Prostate cancer with metastasis. Enantone 6 month DPS is indicated for palliative treatment of advanced hormone-dependent prostate carcinoma.

Abbreviated prescribing information:Indication: Enantone 1-Month DPS 3.75 mg Prostate cancer, endometriosis at genital & extragenital localization (from stage I-IV), premenopausal breast cancer, decrease of myoma volume &/or amelioration of symptoms in uterine myoma, central precocious puberty. Enantone 3-Month DPS 11.25 mg Prostate cancer with metastasis, endometriosis at genital & extragenital localization (from stage I-IV). Treatment of uterine fibroid, concomitantly with Fe therapy for pre-operative haematologic improvement of patients with anaemia caused by uterine leiomyomata. Precocious puberty. Enantone 6-Month DPS 30 mg Palliative treatment of advanced hormone-dependent prostate carcinoma. **Dosage:** Enantone 1-month DPS 3.75 mg subcutaneous injection. Endometriosis for adults, 3.75 mg once every 4 weeks for 6 months. The patient's weight < 50 kg, 1.88 mg may be used.for 6 month. Initiate administration on 1st-5th day after the start of the menstrual period. Central precocious puberty 30-180 mcg/kg once every 4 week. Uterine myoma 1.88 mg once every 4 week. Heavy weight patients or those with markedly enlarged uterus 3.75 mg once every 4 week. Initiate administration on the 1st-5th day after the start of the menstrual period. Prostate cancer & premenopausal breast cancer 3.75mg once every 4 week. Enantone 3-Month DPS 11.25 mg subcutaneous/intramuscular injection. Metastatic prostate cancer 11.25mg every 3 month. Endometriosis 11.25mg every 3 month for 6 month. Uterine fibroid 11.25mg every 3 months for 6 months. Precocious puberty Children <20 kg 5.63mg (half content of pre-filled syringe) once every 3 month. Children ≥20 kg 11.25mg (whole content of pre-filled syringe) once every 3 month. Enantone 6-Month DPS 30 mg subcutaneous once every 6 mnth with interval of 168 days to max 182 days. **Contraindication:** Hypersensitivity to leuprorelin or other GnRH analogues, polylactic acid. Undiagnosed abnormal genital bleeding. Pregnancy, lactation. **Adverse Reactions:** Anaphylactic symptoms. Pituitary apoplexy may develop after initial administration in patients with pituitary adenoma. Depression. Women: Hot flushes, menstrual disorders, vaginal dryness, libido decrease. Men: Transient aggravation of bone pain, ureteral obstruction or spinal cord compression. Hot flushes, impotence, decrease in testes size, nausea, vomiting, edema of lower limbs, general pain, gynaecomastia. Loss of appetite, headache, joint or back pain, muscle weakness, nocturia, dysuria, injection site reactions, increased sweating, tiredness peripheral edema, paraesthesia, sleep disturbances, weight gain.

Reference:
1. Enantone 1 month DPS 3.75mg package insert, ENTDPS1M0814PIHK1. 2. Enantone 3 month DPS 11.25mg package insert, ENTDPS3M0314PIHK1. 3. Enantone 6 month DPS 30mg package insert, ENT6MDPS0613PIHK.

Takeda Pharmaceuticals (Hong Kong) Limited
23 & 24/F, East Exchange Tower
38 Leighton Road, Causeway Bay, Hong Kong
Tel : (852) 2133 9800 Fax : (852) 2856 2728

Enantone® DPS
leuprorelin acetate dual chamber pre-filled syringe

For further information, please consult full prescribing information.

HK/KK/ENA/08/10-2015

In Memory of Dr HUNG Kwan Ngai (1964~2015)

Back in the early 1990's, all of us working in neurosurgery were a bit surprised and happy that there eventually was a newcomer to our specialty at Queen Mary Hospital where there was so much work and yet so few committed. He was described as hardworking with incredible energy and despite his relative juniority could handle emergency reliably and with masterly finesse! Soon after that I was introduced to HUNG Kwan Ngai – a person whom I could only conclude that all these descriptions were indeed understatements.

Kwan Ngai, whom I preferred to address as 洪爺 every time we met was a fighter, an excellent neurosurgeon, an avid reader of wide interests, a reliable colleague, a righteous person and my unforgettable friend.

Although we never worked together in the same department, exchanges and interactions within the local neurosurgical community gave me a clear knowledge of his professionalism. Knowing well the demands and difficulties a neurosurgeon faces, I looked up to him - with his own unabating malady and yet fulfilling all his daily duties with excellence - with nothing but awe and admiration. He, a caring doctor unceasingly aiming at managing his patients better, was aptly an expert in functional neurosurgery that calls for impeccable technical precision and perfectionistic attitude. He was well liked by patients whom he cared for and junior doctors whom he taught.

Yet it was at overseas conferences and studies abroad that I could really fathomed Kwan Ngai as a person. We attended the European Congress at Berlin together in 1995 and two years later during my visit to Professor Wolfgang Koos, an iconic grandfather surgeon at the time, he was there with him as visiting fellow and Kwan Ngai was kind enough to acquaint me with not just the various academic activities but the city of Vienna as well. Chances to talk about things without our trade helped me realize that we did share common hobbies - appreciation of Chinese calligraphy, classical music and collection of limited edition fountain pens, just to name a few. Unlike me, he read a lot and even remembered. To me, he was a walking encyclopedia of history, east and west; common knowledge, broad and deep. Since then we had ample things to talk about apart from the handling of neural tissues!

Thanks to his generous response to my invitation when I served as the President of the Federation of Medical Societies, his expertise was put to good use between 2004 and 2007 at the helm of the Education Committee. Under his leadership, we held numerous very successful educational courses and Annual Scientific Meetings. His effective and decisive management style impressed us all at the Federation and undoubtedly set a very high standard for the rest to follow.

Serving at the Hospital Authority all his career, he clearly understood the challenges colleagues face. Effectiveness of clinical service is limited not simply in terms of human resources but more so in the efficiency of its delivery. In 2011, Kwan Ngai continued his journey to strive for excellence in a broader perspective. He 'unscrubbed' as a surgeon for 2 years and worked at the Hospital Authority Quality and Safety Division and returned to Queen Mary to serve as the Coordinator of Operating Theatre Services. He confided in me that his aim was to work out a better workflow in the operating theatre and eventually might help us all. It would not be easy but he would surely try!

Regrettably, this noble course is now his legacy. 洪爺 left all too suddenly on 30th December 2015, without any pain or suffering. Hong Kong has lost a good doctor, the neurosurgery community an academic, the Federation an outstanding colleague and for me a dear friend! Despite that being relatively short, his life was full; full of love, devotion, gratitude, humour and kindness – characteristics of an outstanding person that will certainly leave indelible impressions on all those who knew him. He is survived by a lovely family – Rosanna, the love of his life and their wonderful son Anthony. May peace be with them always.

Dr Dawson FONG

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	★ Urothelial Carcinoma in Disguise **1**	★ HKMA Council Meeting ★ FMSHK Officers' Meeting **2**	**3**	**4**	**5**	**6**
7	**8**	**9**	**10**	**11**	**12**	★ CME Lecture - Refresher Course for Health Care Providers 2015/2016 **13**
14	**15**	★ HKMA Kowloon West Community Network - Common Medical Emergencies in GP Setting ★ Inter- hospital Rheumatology Meeting 2016 **16**	★ Hong Kong Neurosurgical Society Monthly Academic Meeting –Nature of Craniopharyngioma: Implications on Management, Recurrence and Functional Outcome **17**	★ HKMA Hong Kong East Community Network - Updates on Management of Rheumatic Diseases ★ HKMA Kowloon East Community Network - The Changing Scenario of Chronic Ischemic Heart Disease: Focus on Diabetic Coronary Patients ★ HKMA New Territories West Community Network - Seminar on Management of Common Breastfeeding Problems: What Primary Care Doctors Need to Know and Practice? **18**	**19**	**20**
21	**22**	**23**	**24**	★ FMSHK Executive Committee Meeting ★ FMSHK Council Meeting **25**	**26**	★ MindScape Seminar **27**
★ MindScape Seminar **28**	**29**					

Date / Time	Function	Enquiry / Remarks
1 MON 7:30 PM	**Urothelial Carcinoma in Disguise** Organiser: Hong Kong Urological Association; Chairman: Dr Wayne Chan, KWH; Speaker: Dr Jerry Ng,KWH; Venue: Multi-disciplinary Simulation and Skills Centre, 4/F, Block F, QEH	Ms. Tammy HUNG Tel: 9609 6064 1 CME Point
2 TUE 8:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. SHIH Tai Cho, Louis; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
	FMSHK Officers' Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
13 SAT 2:15 PM	**CME Lecture - Refresher Course for Health Care Providers 2015/2016** Organiser: The Hong Kong Medical Association; Speaker: Dr. Wong Hing Cheong; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Point
16 TUE 1:00 PM	**HKMA Kowloon West Community Network - Common Medical Emergencies in GP Setting** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. WONG Wai Hong, Bruce; Speaker: Dr. LIT Chau Hung, Albert; Venue: Crystal Room IV-V, 3/F., Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Ms. Hana YEUNG Tel: 2527 8285 1 CME Point
6:00PM	**Inter- hospital Rheumatology Meeting 2016** Organiser:The Hong Kong Society of Rheumatology; Chairman: Dr CS LAU; Speaker: Dr. YEUNG Wan Yin; Venue: Hospital Authority Headquarters, Room 205S.	Dr. LEE Ka Lai Tel: 9229 4616 1 CME Point
17 WED 7:30AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Nature of Craniopharyngioma: Implications on Management, Recurrence and Functional Outcome** Organiser: Hong Kong Neurosurgical Society; Chairman: Dr WONG Chi Keung; Speaker: Dr CHAN Yuen Chung, David; Venue: M Block Ground Floor Lecture Theatre, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 1.5 CME Point
18 THU 1:00 PM	**HKMA Hong Kong East Community Network - Updates on Management of Rheumatic Diseases** Organiser: HKMA Hong Kong East Community Network and Hong Kong Society of Rheumatology; Chairman: Dr. YIP Yuk Pang, Kenneth; Speaker: Dr. LEE Tsz Yan, Samson; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00PM	**HKMA Kowloon East Community Network - The Changing Scenario of Chronic Ischemic Heart Disease: Focus on Diabetic Coronary Patients** Organiser: HKMA Kowloon East Community Network; Chairman: Dr. MA Ping Kwan, Danny; Speaker: Dr. TING Zhao Wei, Rose; Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Ms. Hana YEUNG Tel: 2527 8285 1 CME Point
1:00PM	**HKMA New Territories West Community Network - Seminar on Management of Common Breastfeeding Problems: What Primary Care Doctors Need to Know and Practice?** Organiser: HKMA New Territories West Community Network; Chairman: Dr. TSUI Fung; Speaker: Dr. FOK Oi Ling, Annie; Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家), 1/F., Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Ms. Hana YEUNG Tel: 2527 8285 1 CME Point
25 THU 7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
27 SAT 2:00 PM *(28) 10:00 AM*	**MindScape Seminar** Organiser: Body Talk Hong Kong; Speaker: Ms Angie TOURANI; Venue: Karma Consultants, 11fl, Willie Rd, 222-224 de Vous Rd, Central	Ms Angie TOURANI Email: angie@bodytalksystem.com.hk Website: http://www.bodytalksystem.com.hk/mavista/cms/en/bodyTalk_courses/mindscape-Seminar

Upcoming Meeting

17/3/2016 8:00 AM	**Health Care Forum: War on Cancer** Organiser: The Economist Events; Speakers: Kenneth Hartigan-Go, Under-Secretary of Health, Office for Health Regulation, Department of Health, Republic of the Philippines; Chiou Shu-Ti, Director-general, Health Promotion Administration, Ministry of Health and Welfare, Taiwan; Venue: The Ritz-Carlton, Millenia Singapore	Ms. Gloria WONG Tel: 2585 3839 Fax: 2802 7007

Federation Visit to Beijing

The Federation was cordially invited to attend the 25th National Assembly & Centennial Anniversary of the Chinese Medical Association (CMA) on 14-16 December 2015. Dr Mario CHAK, President of the Federation of Medical Societies of Hong Kong (FMSHK), together with the Immediate Past President Dr Raymond LO attended the assembly at the Great Hall of the People in Beijing. We would like to express our sincere gratitude to the CMA for their invitation and kind hospitality.

Annual Dinner 2015- Federation on Broadway

On 31 December 2015, the traditional Annual Dinner of the Federation of Medical Societies of Hong Kong was held at the Sir Run Run Shaw Hall of the Hong Kong Academy of Medicine, to celebrate New Year's Eve with our members, friends and families. The dinner was a resounding success that exemplified the Federation spirit, attended by over 300 guests from our member societies and partners from the medical & healthcare communities.

A glamorous venue and a programme of wonderful music epitomized the theme, Federation on Broadway. We were delighted to witness exquisite performances by Ms Becky Lee (李璧琦), Ms Corinna Chamberlain (陳明恩) and Ms Silian Wong (王靖喬), and last but not least, our special guest, Mr Peter Lai (黎彼得), who led us in the Federation song. The Broadway Costume Prize, King and Queen of Karaoke and Dance Fever Competition provided a wealth of entertainment and fun.

We were privileged to be joined by many distinguished guests: the Under Secretary for Food and Health, Prof Sophia CHAN; Chairman of the Hospital Authority, Dr John LEONG; President of the Academy of Medicine, Dr Donald LI; Honorary Secretary of the Academy of Medicine, Dr LAU Chor-chiu; The Hon Dr Ka-lau LEUNG; The Hon Prof Kwok-lun LEE and Prof Diana LEE; The Hon Dr LEONG Che-hung and Dr Lillian LEONG; Prof Gabriel LEUNG; Dr CHEUNG Tse Ming and Dr Cissy YU. The presence of these honorable guests helped light up the event and we express our heartfelt thanks to them.

This year, fabulous prizes worth up to $100,000 were awarded, including the Luxury Prize for Uniworld Enchanting Danube Package and the Premier Prize of a 15 Day Panama Canal Cruise. Guests were fabulously entertained by bingo games, instant fun photo taking, wine booth, harp performance, and the climax of the night – countdown to the New Year 2016.

Much excitement and joy shared by all those present made for a memorable night. We would like to express our sincere gratitude to all our sponsors, and thank all our guests for joining us on this special occasion.


Federation on Broadway
BROADWAY

Answers to Radiology Quiz

Answer:

1. A curvilinear calcific rim is seen at the left paraspinal region, highly suggestive of a calcified wall of an abdominal arterial aneurysm. (Figure 2) No radio-opacity is seen to suggest presence of a urinary tract stone. Bilateral psoas shadows appear normal. Degenerative changes are also seen in the lumbar spine.

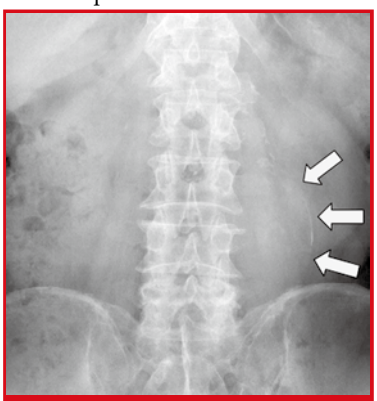


Figure 2: Calcific rim of AAA (white arrows)

2. Urgent referral for symptomatic AAA is warranted.

3. Further imaging with computed tomography (CT) is required for assessment of AAA complications. CT is the gold standard imaging due to the speed of the examination and widespread availability of CT.

Patient progress:

The patient was urgently referred for symptomatic AAA. Urgent contrast CT revealed a fusiform infrarenal AAA with maximal transverse diameter of 8.7x7.3cm. Circumferential thrombus was observed with vague peripheral crescent of hyperdensity, suspicious of bleeding within the mural thrombus. Periaortic stranding was also evident. No contrast extravasation was observed (Figures 3 to 6). Overall features were suspicious of impending AAA rupture. The patient underwent emergency EVAR with an excellent result and resolution of symptoms. (Figure 7).

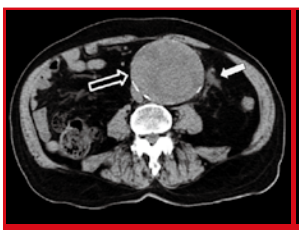


Figure 3: Vague peripheral crescent of hyperdensity, suspicious of bleeding within the mural thrombus (black arrow). Periaortic stranding is also seen (white arrow)

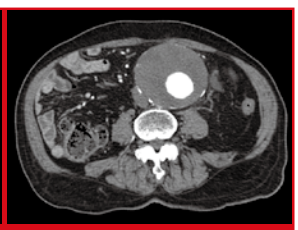


Figure 4: Post-contrast CT did not reveal contrast extravasation.

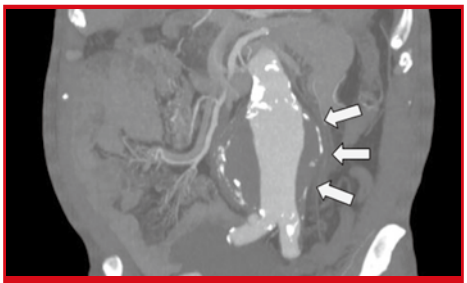


Figure 5: Maximum intensity projection (MIP) reveals mural calcifications corresponding to findings on AXR (white arrows).

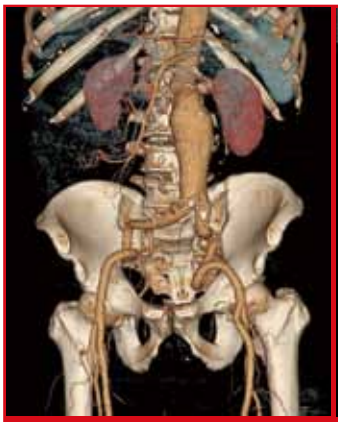


Figure 6: Volume rendering image of the same patient.

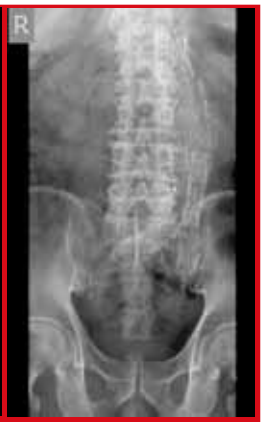


Figure 7: Post-EVAR AXR. Note that the thin calcified rim is still observed on the left aspect.

Discussion:

Abdominal aortic aneurysm (AAA) is a focal dilatation of the abdominal aorta that is 50% greater than the proximal normal segment or >3 cm in maximum diameter.

There is increased prevalence with increasing age, and a male predominance (M:F = 4:1).

In Hong Kong, the annual incidence of AAA is 13.7 per 100,000 population and 105 per 100,000 in those aged 65 and above. About 10% of AAAs present when they rupture.

Common causes include atherosclerosis, inflammatory abdominal aortic aneurysm, chronic aortic dissection, connective tissue disorders (e.g.Marfan syndrome, Loeys-Dietz syndrome and Ehlers Danlos syndrome), mycotic aneurysms and vasculitis (e.g. Takayasu arteritis).

AAAs are usually asymptomatic until complicated by leakage or rupture. Uncommon presentations of an unruptured aneurysm include abdominal or back pain or presence of a pulsatile abdominal mass.

Treatment is suggested when an aneurysm exceeds 5.0cm in women and 5.5 - 6.0cm in men due to a

Answers to Radiology Quiz

significantly increased risk of rupture. Treatment is also considered if an aneurysm expands by >10mm per year even if it remains <5.0cm because of the significant risk of rupture.

Treatment options include endovascular aneurysm repair (EVAR) or open surgical repair.

References

1. *Rakita D, Newatia A, Hines JJ, Siegel DN, Friedman B. Spectrum of CT findings in rupture and impending rupture of abdominal aortic aneurysms. Radiographics. 2007 Mar-Apr;27(2):497-507.*
2. *Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. J Vasc Surg 2003;37(2):280–284*
3. *Arita T, Matsunaga N, Takano K, et al. Abdominal aortic aneurysm: rupture associated with the high-attenuating crescent sign. Radiology 1997;204(3):765–768*
4. *Mehard WB, Heiken JP, Sicard GA. High-attenuating crescent in abdominal aortic aneurysm wall at CT: a sign of acute or impending rupture. Radiology 1994;192(2):359–362*
5. *Cheng SW1, Ting AC, Tsang SH.Epidemiology and outcome of aortic aneurysms in Hong Kong. World J Surg. 2003 Feb;27(2):241-5.*

Dr Kenneth KY CHEUNG

Department of Radiology, Queen Mary Hospital.

The Economist Events

HEALTH CARE FORUM

WAR ON CANCER

MARCH 17TH 2016 • SINGAPORE

KENNETH HARTIGAN-GO
Under-secretary of health
Office for health regulation
Department of health
Republic of the Philippines

CHIOU SHU-TI
Director-general
Health promotion administration
Ministry of health and welfare
Taiwan

NELLY ENWEREM-BROMSON
Director, division programme of action for cancer therapy and department of technical co-operation
International Atomic Energy Agency

OPHIRA GINSBURG
Medical officer
management of noncommunicable diseases
World Health Organisation

RICHARD SULLIVAN
Professor, cancer policy and global health
Kings College London
and director
Kings Institute of Cancer Policy

MASUM HOSSAIN
Regional president
Asia-Pacific
Pfizer Oncology

How can countries in Asia manage the rising costs of cancer care?

Join leaders from government, industry and academia to learn about practical and cost-effective measures being used to attack cancer in Asia, and discuss how they can be improved and implemented for the benefit of patients.

Register today and save

USD380

Subscribers of The Federation of Medical Societies of Hong Kong can enjoy a 20% discount on the standard price (Code: 3531FMSHK at check-out)

Apply to attend:
asiaevents@economist.com
+852 2585 3312

Join the conversation
@EconomistEvents #EconWaronCancer

waroncancer_asia.economist.com

Platinum sponsor: Pfizer

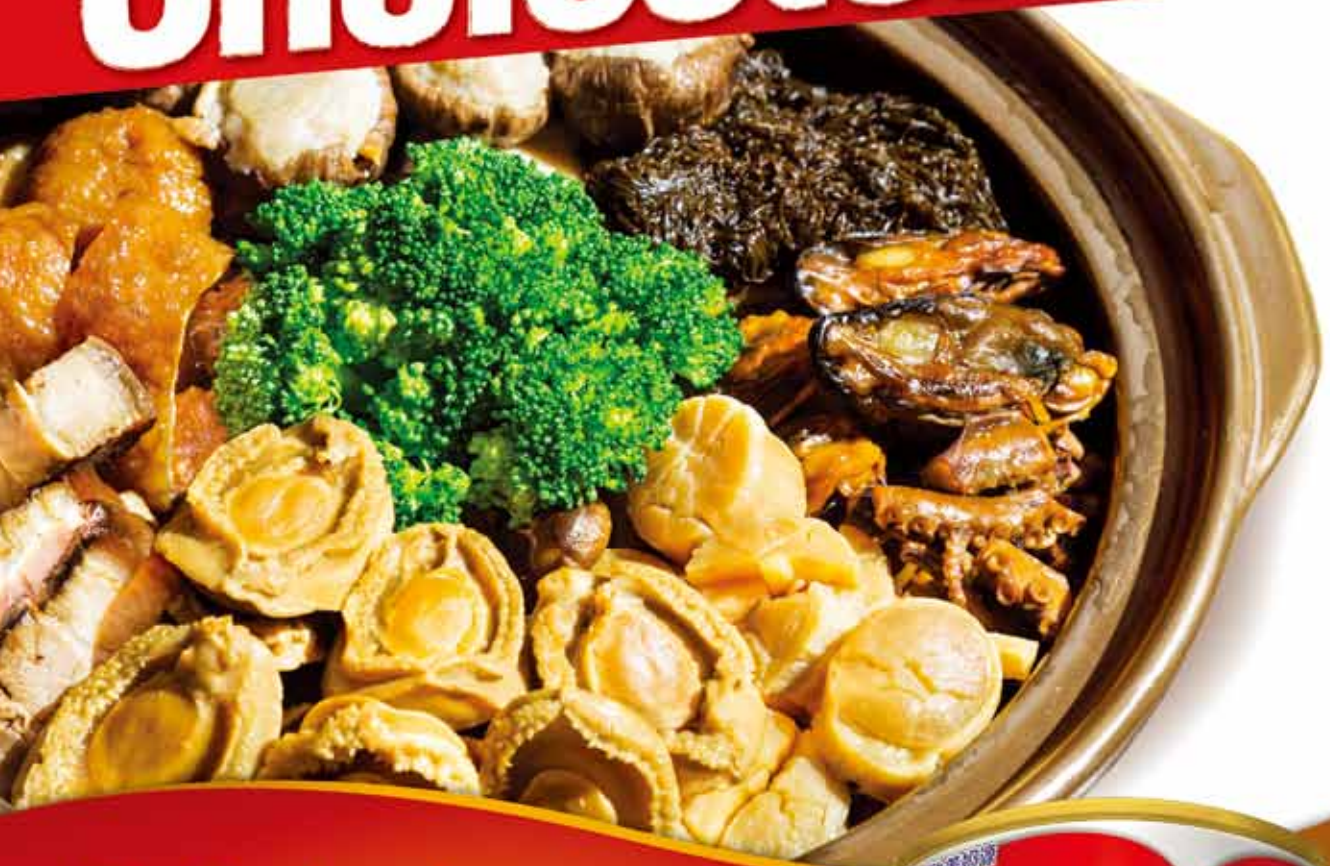
Gold sponsors: AMGEN, Takeda

Silver sponsors: abbvie, imshealth, Roche

Supporting medical centre: PCC

Supporting organisation

Elevations in Cholesterol?



Phytosterols

Proven efficacy in reducing LDL cholesterol+

- Every 2 cups of milk contain **1.5 g phytosterols** and 259 mg omega-3 fatty acids
- **Clinical Proven** to reduce up to 10% LDL cholesterol within 3 weeks+
- Additive effects with statin and omega-3 fatty acids[1-2]

+ CL Cheung, BMY Cheung, et al. Randomised controlled trial of the effect of phytosterol-enriched low-fat milk on lipid profile in Chinese. J HK Coll Cardiol 2015;23:94.
1. Simons LA. Additive effect of plant sterol-ester margarine and cerivastatin in lowering low-density lipoprotein cholesterol in primary hypercholesterolemia. Am J Cardiol 2002;90:737-740.
2. Micallef MA, Garg ML. The lipid-lowering effects of phytosterols and (n-3) polyunsaturated fatty acids are synergistic and complementary in hyperlipidemic men and women. J Nutr 2008;138:1086-1090.